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LOCALLY RECURRENT RECTAL CANCER – ASPECTS ON MANAGEMENT, SURGERY AND OUTCOME

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Locally recurrent rectal cancer – aspects on management, surgery and outcome

THESIS FOR DOCTORAL DEGREE (Ph.D.)

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ABSTRACT

Locally recurrent rectal cancer (LRRC) is a severe condition associated with a high morbidity and mortality, affecting about 150-200 people/year in Sweden. After improvements in management and treatment of primary rectal cancer (RC), including an amelioration and standardisation of surgical technique, improved preoperative staging, addition of preoperative radiotherapy (RT), implementation of multidisciplinary team conferences and postoperative surveillance programmes, the rate of LRRC has decreased dramatically from 30-40% to 5-15%. A curative surgical resection is necessary for a favourable prognosis and five-year survival rates of more than 60% have been reported after curative surgery. However, when looking at all patients with LRRC, the survival rate drops below 10%. The aim of this thesis was to learn more about the characteristics, management and outcome of patients with LRRC in Sweden.

Paper I aimed at investigating whether the time interval from primary surgery of RC to diagnosis of LRRC had any impact on survival after LRRC diagnosis. Population-based data on patients operated for primary RC during the period 1995-2002 and with a diagnosis of LRRC as first event reported to the Swedish Colorectal Cancer Registry (SCRCR) were accessed from the registry. 386 patients were included, of which 25% had an early LRRC (ELR) and 75% had a late LRRC (LLR). Patients with a stage III primary tumour and non-irradiated patients were significantly more common in the ELR group. Factors that influenced survival were age, stage of primary tumour and surgical resection of the LRRC. Time to diagnosis of LRRC did not influence survival and should not be taken into account in treatment decisions of LRRC patients.

The aim of **paper II** was to assess what factors affect treatment intention in patients with LRRC. Medical records of patients defined by the same criteria as in paper I were collected and analysed. 426 patients were included, of which 35% had been treated with curative intent and 65% with palliative intent. Factors significantly associated with palliative treatment intention were age ≥ 80 years, presence of symptoms and a non-central location of the LRRC. The same factors also increased the risk of death among patients treated with curative intent. Five-year survival was 23% for patients treated with curative intent and 9% for all LRRC patients. The results present a congruence between factors predictive for treatment and prognostic factors, indicating an adequate selection for treatment.

In **paper III**, an analysis of time trends, regional variations and prognosis of the same patients as in paper II was performed. 28% of the patients were treated with tumour resection with curative intent. No significant time trends or regional variations were seen regarding treatment intention or resection margins after surgery for LRRC. The proportion of patients with non-central recurrences increased over time. Patients with a centrally located tumour were more likely to have a radical tumour resection. Five-year survival rates were 43% for patients treated with R0 resection and 14% after R1 resection. The results confirm that negative resection margins are crucial for a favourable prognosis in patients with LRRC.

In **paper IV**, details on surgical treatment of the LRRC in the patient cohort included in paper II and III were evaluated. 35% were treated with tumour resection, 19% had surgery without tumour resection and 20% were treated with best supportive care. Abdominoperineal resection was the most commonly performed resection procedure, performed in 49% of the abdominally resected patients. In total, 49% of the patients had a multi-organ resection and another 10% had a total pelvic exenteration. Complications were more common after tumour resection than after surgery without tumour resection, but the postoperative mortality was significantly higher among non-resected patients. Complications should be avoided, possibly by a better selection for surgery.

LIST OF SCIENTIFIC PAPERS

I. Time to local recurrence as a prognostic factor in patients with rectal cancer

K Westberg, G Palmer, H Johansson, T Holm, A Martling

European Journal of Surgical Oncology

2015; 40(5):659-666

II. A population-based study of factors predicting treatment intention in patients with locally recurrent rectal cancer

K Westberg, G Palmer, F Hjern, C Nordenvall, H Johansson, T Holm,

A Martling

British Journal of Surgery

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III. Management and prognosis of locally recurrent rectal cancer – a national population-based study

K Westberg, G Palmer, F Hjern, H Johansson, T Holm, A Martling

Submitted

IV. A population-based study of surgical treatment with and without tumour resection of patients with locally recurrent rectal cancer

K Westberg, G Palmer, F Hjern, T Holm, A Martling

Manuscript

LIST OF ABBREVIATIONS

AJCC	American Joint Committee on Cancer
AL	Anastomotic leak
APE	Abdominoperineal excision
APR	Abdominoperineal resection
AR	Anterior resection
ASA	American Society of Anaesthesiologists
BSC	Best supportive care
CC	Colon cancer
ChT	Chemotherapy
CI	Confidence interval
CRC	Colorectal cancer
CRM	Circumferential resection margin
CRT	Chemoradiotherapy
CT	Computed tomography
DVT	Deep venous thrombosis
ELAPE	Extra levator abdominoperineal excision
ELR	Early local recurrence
EMVI	Extramural vascular invasion
FAP	Familial adenomatous polyposis
Gy	Gray
HA	Hartmann's procedure
HR	Hazard ratio
IBD	Inflammatory bowel disease
IORT	Intraoperative radiotherapy
LLR	Late local recurrence
MAP	MYH-associated polyposis
MDT	Multidisciplinary team
MRF	Mesorectal fascia
MRI	Magnetic resonance imaging
OR	Odds ratio
PE	Pelvic exenteration
QoL	Quality of life
RT	Radiotherapy
SCRCR	Swedish Colorectal Cancer Registry
TME	Total Mesorectal Excision
TNM	Tumour Node Metastasis staging system
UICC	Union for International Cancer Control
WHO	World Health Organisation

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1 BACKGROUND

1.1 RECTAL CANCER

1.1.1 Epidemiology

Colorectal cancer (CRC) is the third most common type of cancer worldwide, with 1.4 million new cases each year and 700 000 deaths in 2012². The highest incidence of CRC is found in high-income developed countries, particularly in Australia, New Zealand, Europe and Northern America, while the rates are low in Africa and South and Central Asia³. The differences in geographical distribution are most likely explained by a varying exposure to life-style related risk factors². CRC is more common in men than in women throughout the world, for unknown reasons. The life-time risk of CRC in the general population is 4-5%⁴. The disease is uncommon before 50 years of age and the incidence thereafter rises with age. The global burden of CRC is increasing and by 2030, 2.2 million new cases and 1.1 million CRC-related deaths are expected. However, a trend of decreasing both incidence and mortality is observed in Australia, Iceland, New Zealand, Japan and the USA, while an increasing incidence and reduced mortality is seen in Northern and Central Europe². The decreasing mortality rate in these countries is thought to be attributed to increased CRC screening, altered risk factor pattern and improved treatment⁵.

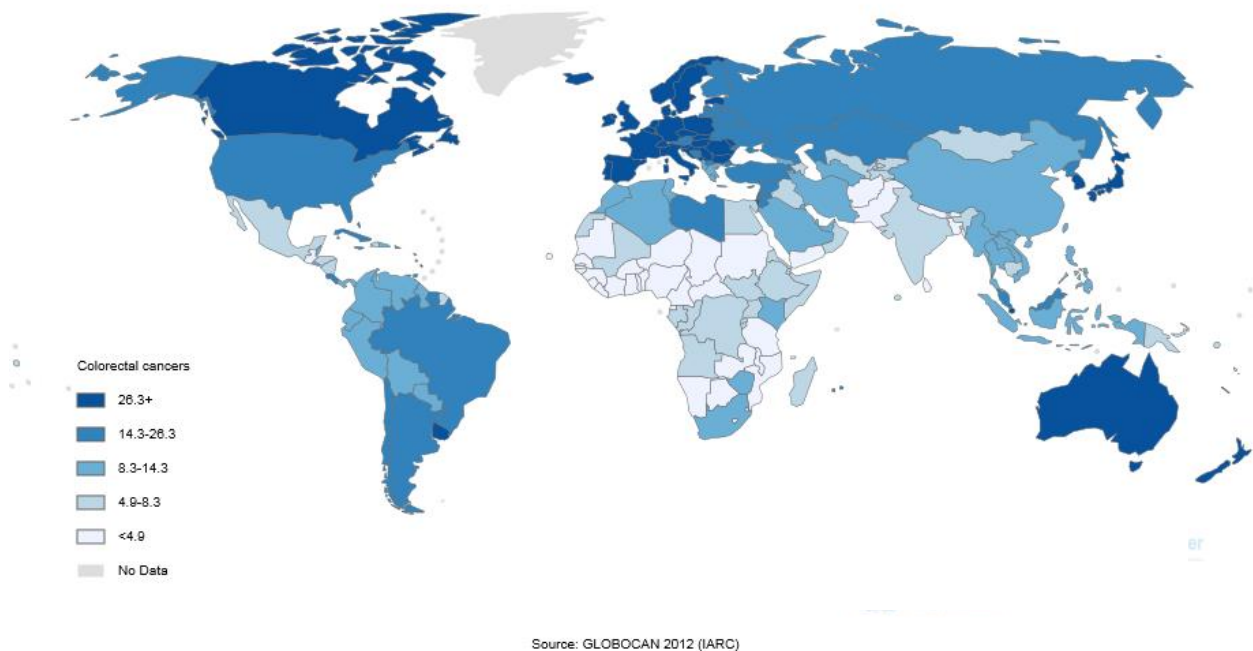


Figure 1 Map illustrating the age-standardised incidence of colorectal cancer per 100 000 inhabitants for men and women in 2012. Reprinted with permission from GLOBOCAN 2012, International Agency for Research on Cancer⁶

In Sweden, about 6000 new cases of CRC are diagnosed each year and of these, approximately one third have rectal cancer (RC). Less than half of the patients (40%) are women. The overall incidence is slowly increasing, while the age-standardised incidence has been stable over the last 15 years. The relative survival has increased dramatically during the last 30 years. Current five year-survival in men is 63% and 64% in women and the 10 year-survival is 54% and 58% respectively⁷.

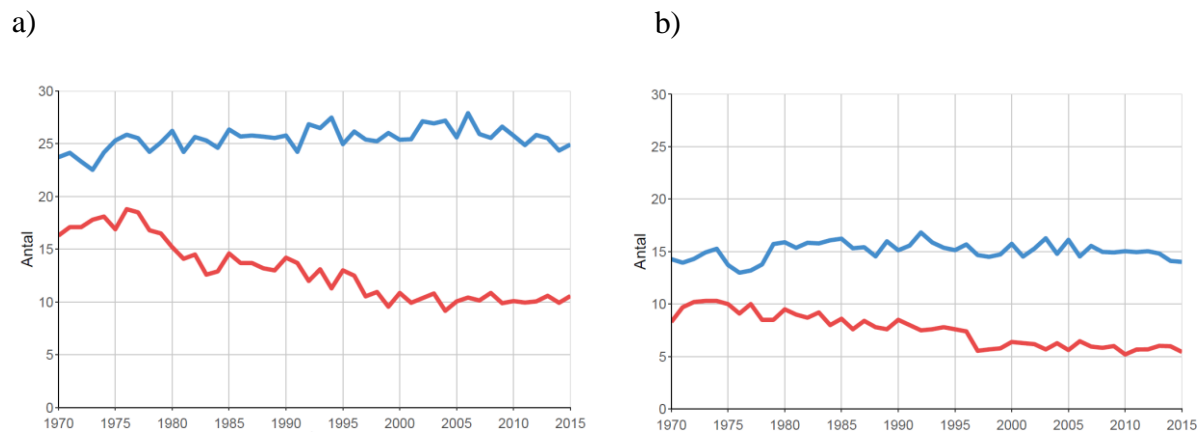


Figure 2 Age-standardised incidence (blue) and mortality (red) per 100 000 inhabitants in Sweden between 1970-2015 among a) men and b) women ¹. Reprint with permission.

1.1.2 Pathogenesis and risk factors

Sugarbaker et al suggested in 1985 that most malignant colorectal tumours arise from benign adenomas⁸. After further exploration of the process, it has become widely accepted that adenomas are the precursors of colorectal cancer, which develops through a multistep process triggered by mutations leading to the activation of oncogenes and inactivation of tumour suppressor genes^{9,10}. It is estimated that 95% of colorectal neoplasms develop from benign adenomas. However, adenomas are common, present in 15-35% of asymptomatic adults^{11,12}, and only 10% become neoplastic¹³. The risk of malignification is related to both the number and size of the adenomas. Since the development from adenoma to colorectal neoplasm takes several years, early finding may prevent a fulminant development of colorectal cancer. Screening programs leading to early detection and removal of adenomas have been shown to reduce the risk of CRC and prolong overall survival ¹⁴⁻¹⁸.

Among known non-modifiable risk factors for CRC, age, hereditary syndromes and a history of inflammatory bowel disease (IBD) are the most important ones. About 20-25% of CRC cases are caused by inherited factors and 5-10% are the result of known genes predisposing for a colorectal syndrome, including the Lynch syndrome, familial adenomatous polyposis (FAP) and MYH-associated polyposis (MAP) as the most common^{19,20}. The remaining 75-80% of all CRC tumours arise sporadically, without genetic predisposition to the disease. The association

between IBD and CRC is well supported and the risk increases with duration of the disease, with 8% risk at 20 years and 18% risk at 30 years of IBD^{21,22}. Much interest has been directed towards the influence of lifestyle factors on the risk of developing CRC, but few significant factors have been verified. Obesity and a high intake of red meat, tobacco and alcohol are factors suggested to increase the risk of colorectal cancer, while a high fibre intake, physical activity and long-term use of aspirin are factors believed to have a protective effect²³⁻²⁵.

1.1.3 Anatomy

Minor variations in the definition of the rectum exist, but it is generally described as the final 15 cm of the large bowel, beginning at the rectosigmoid junction and ending at the anal verge. In surgical practice, the sacral promontory is regarded as the upper landmark from which the rectum extends down towards the pelvic floor, where it transforms into the anal canal. The rectum is enfolded by the mesorectum, a fatty lymphovascular tissue, which in turn is surrounded by the avascular perirectal fascia. The mesorectum is thicker posteriorly and laterally and thins out as it reaches the anorectal junction²⁶. The main arterial blood supply derives from the inferior mesenteric artery, which arises from the aorta. After giving off branches to the left colon and sigmoid, the remaining branch named the superior rectal artery subdivides into right and left branches which supply the rectum. The middle and inferior hemorrhoid arteries both derive from the internal iliac artery and together supply the distal portion of the rectum. Knowledge of vascular anatomy is essential in colorectal cancer surgery, as the lymphatic drainage and potential cancer spread follows the same routes as the large vessels²⁷.

The upper third of the rectum is circumferentially surrounded by peritoneum, while the middle third is covered anteriorly by peritoneum and posteriorly has a retroperitoneal position. The most distal part of the rectum, below the rectouterine pouch, is completely retroperitoneal. The rectum has close proximity to other organs and is anteriorly limited by the prostate, seminal vesicles, vas and urinary bladder in men and the upper vagina and uterus in women, posteriorly by the sacrum, coccyx and sacral nerves and laterally by the ureters, iliac vessels and the lateral pelvic wall. It is also common that part of the small intestine, the sigmoid colon or the ovaries fill out the remaining intraperitoneal space of the lesser pelvis leading to tumour engagement of these organs in cases of locally advanced RC or LRRC²⁷. The proximity to other vital organs as well as the natural narrowness of the pelvis has a high impact on the planning and performance of rectal cancer treatment, both regarding surgery and radiotherapy (RT).

The pelvic floor resembles a muscular mat that keeps pelvic organs in place, only allowing passage of the rectum, urethra and (in women) vagina and maintaining urine and faecal continence. The largest constituent muscle, the puborectal muscle, forms a loop around the rectum and its most adjacent part makes up the external anal sphincter, which is innervated by sympathetic fibres and has a vital function in defecation and anal continence. The internal sphincter is innervated by parasympathetic fibres and is formed by a thickened part of the muscular layer of the bowel wall inside the external sphincter.

1.1.4 Preoperative assessment and staging

1.1.4.1 Clinical investigation

Common initial symptoms of RC are altered bowel habits, rectal bleeding and incomplete bowel evacuation, whereas anaemia, abdominal pain, anal incontinence, weight loss and fatigue are symptoms of a more advanced disease. Since the introduction of screening programmes with faecal blood test and/or colonoscopy in healthy individuals, a number of patients are today asymptomatic at time of diagnosis. After clinical examination with rectal palpation, a rectoscopy and a colonoscopy with biopsies from the visualised tumour are often the next steps of the assessment. A colonoscopy with biopsies is usually sufficient for a diagnosis and is also important to rule out synchronous tumours in the colon. An examination with a rigid rectoscope, however, serves an additional purpose, allowing for a more reliable estimation of the distance of the tumour from the anal verge. According to international guidelines, the tumour height is then classified as either low (0-5 cm), median (6-10 cm) or high (11-15 cm)²⁸. The height of the tumour is one of many factors that determines further type of treatment.

1.1.4.2 Computed tomography

Contrast-enhanced computed tomography (CT) of the chest and abdomen is the method of choice to demonstrate or rule out synchronous distant metastases, primarily in the liver or lungs. The sensitivity for the detection of pulmonary metastases by CT is high, 99%. The transition from the previously used chest x-ray to CT has however entailed an increased finding of lung lesions that are too small to allow for a diagnosis. These indeterminate lesions are found in 4-24% of the patients and may lead to several additional examinations, but more than 70% of the lesions lack clinical significance²⁹. For the detection of liver metastases, the sensitivity and specificity is good (74-84% and 95-96%), but in case of uncertainty, magnetic resonance imaging (MRI) is recommended as it has a higher accuracy, particularly in smaller lesions^{30,31}. The sensitivity to predict the distance of the rectal tumour to mesorectal fascia (MRF) is however low, below 50%, and therefore CT should not be used for local staging³².

1.1.4.3 Magnetic resonance imaging

MRI has become an indispensable clinical instrument for the staging and evaluation of rectal tumours. A correctly performed high resolution T2-weighted MRI can adequately stage a rectal cancer, and thereby facilitate treatment selection. It may identify tumour-related high-risk features and is as a reliable instrument for both the selection of patients for neoadjuvant treatment and evaluation of the same treatment³³⁻³⁵. MRI allows for an evaluation of tumour depth (T-stage), lymph nodal involvement (N-stage), relation to the mesorectal fascia (MRF), extramural venous invasion (EMVI) and presence of tumour deposits. The T-staging mainly helps at pointing out early, superficial tumours where organ-sparing treatment may be possible as well as advanced tumours demanding neoadjuvant treatment³⁴. N-staging is based on the number of regional lymph nodes with suspected neoplastic growth. It has been shown that it is not the nodal size but rather the nodal shape, with findings of a mixed signal intensity of the node combined with an irregular border contour, that predicts a positive pathologic finding³⁶.

The MRF represents the surgical resection plane and the relation of the tumour to MRF is an important predictive marker of a clear circumferential resection margin (CRM). The accuracy of a pelvic MRI in the staging of T-, N-, and CRM-involvement has been manifested in several studies³⁷⁻³⁹. In a meta-analysis by Al-Sukhni *et al.*, including 21 studies, the sensitivity for T-stage was 87% and for N-stage and CRM-involvement 77% each. The specificity was highest for predicting CRM involvement (94%) and somewhat lower for predicting T-stage (75%) and N-stage (71%)⁴⁰. In summary, MRI is regarded to have a very high predictive value in the assessment of positive or negative CRM, and a lower but still good value for the prediction of lymph node staging.

MRI interpretation and staging of locally recurrent rectal cancer (LRRC) is more demanding than ordinary RC staging. One of the challenges in LRRC is to distinguish tumour regrowth from fibrotic scar tissue. Diffusion-weighted imaging has been suggested as a complementary tool to facilitate this assessment but is not fully implemented in clinical practice yet^{41,42}.



Figure 3 MRI-scan of patient with local recurrence, tumour indicated

1.1.4.4 PET-CT

In (FDG)PET-CT (Fluorodeoxyglucose Positron Emission Tomography-Computed Tomography), the increased metabolism of neoplastic cells is used for the tracing of tumours. A radioactive isotope, incorporated with a glucogen (FDG), is injected into the patient, metabolised in the tumour cells and detected by the PET-scanner⁴³. The integrated PET-CT evaluation provides additional knowledge of the exact anatomic location of the potential neoplastic lesion. The method may be useful as a complement to standard preoperative assessment, especially for diagnosis of indeterminate, potentially metastatic lesions⁴⁴. Mucinous tumours, however, have a poorer FDG uptake, which is why this type of lesions may be missed⁴⁵. The method may accurately evaluate treatment response after CRT and is a useful tool for treatment selection, but is not as reliable for stating a complete response⁴⁶.

1.1.5 Pathological staging

Postoperative pathological staging is important, since it evaluates the surgical quality and prognosis and forms the basis for a decision of whether adjuvant treatment should be given. Several parallel staging systems are currently used in clinical practice. The previously used Dukes' classification system has today been replaced by the TNM-system, developed by the Union for International Cancer Control (UICC) and the American Joint Committee on Cancer (AJCC). The three categories T (tumour depth), N (lymph node status) and M (metastasis) are evaluated separately and the staging provides the basis for clinical treatment decisions. For prognostic calculations, a concluding assessment of the TNM is converted into a numeric stage (I-IV). The TNM-system is regularly revised and updated. The currently used 7th edition was released in 2009⁴⁷.

Table 1 TNM-classification of colorectal cancer, 7th edition⁴⁷.

TNM		
Primary tumour (T)	TX	Primary tumour cannot be assessed
	T0	No evidence of primary tumour
	Tis	Carcinoma in situ: intraepithelial or invasion of lamina propria
	T1	Tumour invades submucosa
	T2	Tumour invades muscularis propria
	T3	Tumour invades through the muscularis propria into pericorectal fat
	T3a	Minimal invasion <1mm beyond the borders of the muscularis propria
	T3b	Slight invasion 1-5 mm beyond the borders of the muscularis propria
	T3c	Moderate invasion 5-15 mm beyond the borders of the muscularis propria
	T3d	Extensive invasion >15 mm beyond the borders of the muscularis propria
	T4a	Tumour penetrates to the surface of visceral peritoneum
	T4b	Tumour directly invades or is adherent to other organs and structures
Regional lymph nodes (N)	NX	Regional lymph nodes cannot be assessed
	N0	No regional lymph node metastasis
	N1	Metastasis in 1-3 regional lymph nodes
	N1a	Metastasis in 1 regional lymph node
	N1b	Metastasis in 2-3 regional lymph nodes
	N1c	Tumour deposit(s) in the subserosa, mesentery or non-peritonealised pericolic or perirectal tissues without regional nodal metastases
	N2	Metastasis in 4 or more regional lymph nodes
	N2a	Metastasis in 4-6 regional lymph nodes
	N2b	Metastasis in 7 or more regional lymph nodes
Distant metastases (M)	MX	Distant metastasis cannot be assessed
	M0	No distant metastasis
	M1	Distant metastasis
	M1a	Metastasis confined to one organ or site
	M1b	Metastasis in more than one organ/site or the peritoneum

Table 2 Staging of colorectal cancer, according to the American Joint Committee on Cancer, 7th edition

Stage	T	N	M	Dukes'
0	Tis	N0	M0	-
I	T1	N0	M0	A
I	T2	N0	M0	A
IIA	T3	N0	M0	B
IIB	T4a	N0	M0	B
IIC	T4b	N0	M0	B
IIIA	T1-T2	N1/N1c	M0	C
	T1	N2a	M0	C
IIIB	T3-T4a	N1/N1c	M0	C
	T2-T3	N2a	M0	C
	T1-T2	N2b	M0	C
IIIC	T4a	N2a	M0	C
	T3-T4a	N2b	M0	C
	T4b	N1-N2	M0	C
IVA	any T	any N	M1a	-
IVB	any T	any N	M1b	-

1.1.6 The Swedish Colorectal Cancer Registry

The Swedish Colorectal Cancer Registry (SCRCR) is a national registry, founded by the National Board of Health and Welfare in 1995 with the intention to monitor management and treatment in patients with CRC. Prospective reporting of clinical data of all patients with diagnosed adenocarcinomas is mandatory for surgeons, oncologists and pathologists. Diagnoses made during autopsy are exempted. Initially, only data on patients with RC were reported, but since 2007, the registry also holds data on patients with colon cancer (CC). Up to 2016, 37 000 patients had been included in the SCRCR and the coverage rate for RC patients is estimated to 99%^{1,48}. Reported data include patient and tumour characteristics, date of surgery, type of surgery, type of neoadjuvant and adjuvant treatment, complications of surgery, resection margins, pathologic tumour details, follow-up data at three and five years after primary surgery, diagnosis of local recurrence and diagnosis and location of distant metastases⁴⁹. Data on management and treatment of patients with LRRC are not reported.

The registry has been validated at several occasions⁴⁹⁻⁵². In 1998, the first validation was performed, showing a discrepancy of less than 5% concerning the core variables type of surgery, tumour stage, postoperative mortality, perioperative perforation and anastomotic leakage (AL)⁴⁹. In another validation, directed specifically towards the complications, it was found an adequate reporting of major complications but an underreporting of minor complications, *i.e.* wound infections⁵⁰. Jörgren *et al.* agreed on a high validity (<10%

discrepancy) of the registry on main variables but that 11% of the LRRC registrations were false⁵². In summary, data have been considered to be of good quality concerning patient, tumour and treatment data but there is an underreporting of complications and follow-up data⁴⁹⁻⁵¹. Every person working with data from the SCRCR is encouraged to report any misclassifications that are found. This makes the registry a living document, where changes are continuously incorporated. Annual reports of SCRCR data are published online and are frequently used for the evaluation and improvement of rectal cancer management on both national, regional and local (hospital) levels. There is a lively research activity attached to the registry, resulting in close to 100 publications up to the present and an additional number of on-going projects⁵³.

1.1.7 Multidisciplinary therapy conference

After completing the preoperative assessment, all patients with CRC should be individually discussed at a multidisciplinary team (MDT) conference. In the MDT discussion, details of the current tumour are processed together with background data, such as co-morbidity, previous treatment, patient's preference and social situation. Both pre- and postoperative discussions are warranted. The team may have different compositions but the participation of surgeon, oncologist, pathologist and radiologist is recommended as a minimum⁵⁴. The meetings not only facilitate communication between different disciplines but have also proven to improve both the quality of assessment and the outcome of surgery. One study showed a significant reduction in the rate of patients operated with a positive CRM after the implementation of preoperative MDT meetings and another demonstrated an improved quality of the preoperative assessment and staging^{55,56}. In a Swedish population-based study it was shown that the practice of MDT conferences combined with an increased staging with MRI more than doubled the rate of R0 resections⁵⁷. The routine use of MDT is today implemented in many cancer disciplines worldwide^{58,59}.

Regarding patients with LRRC, few studies of the isolated effect of an MDT have been performed. It has however been stated that a multidisciplinary approach is of even greater importance in these complex patients, and there is reason to believe that MDT conferences facilitates this, particularly through a better selection for surgery⁶⁰.

1.1.8 Neoadjuvant treatment

Neoadjuvant treatment, also called preoperative treatment, may be given as either RT alone or as a combination of chemotherapy and RT, so called chemoradiotherapy (CRT). The purpose of RT is either to kill potential tumour cells located close to the tumour itself, or to initiate a shrinkage, a so-called downstaging, and thereby convert a large inoperable tumour into a smaller, resectable one. The purpose of a combined treatment with CRT is to potentiate the effect of RT.

Comprehensive research during the last 30 years has led to an increased knowledge about the effects of RT in patients with RC and implementation of the results has reduced the rate of LRRC significantly⁶¹. The Uppsala trial investigated whether RT should be given pre- or postoperatively. 471 patients with stage II and III RC were randomised to preoperative short-course (5x5 Gy) RT or postoperative long-course (2x30 Gy) RT⁶². The study showed a lower LRRC rate in patients irradiated preoperatively, but there was no difference in survival. In the Stockholm I trial, the aim was to compare the oncological results for patients treated with short-course (5x5 Gy) RT followed by surgery with patients treated with surgery alone. The results showed a significantly lower LRRC rate in the RT-group, 16 vs 30%, but a higher risk of early postoperative mortality, especially among elderly⁶³. The same tendency was observed in the Dutch TME-trial⁶⁴. Therefore, the Stockholm II and the Swedish Rectal Cancer Trial were initiated with an adjusted protocol, in order to lower the postoperative morbidity and mortality among RT patients while maintaining the reduced LRRC rate^{65,66}. The goals were achieved and an increased cancer-specific survival rate was also seen.

Despite the improved results, the mortality however remains high and there is reason to believe that the survival could be improved if time to surgery is delayed. This hypothesis is being explored in the Stockholm III trial and the recently published first results indicated a significantly lower risk of postoperative complications after short-course RT with delayed surgery compared to the same RT-regime followed by immediate surgery⁶⁷.

Finally, a few trials have been performed investigating the value of a combined treatment with CRT versus RT alone^{68,69}. The combined regime had the best results in terms of both local relapse and survival, particularly for locally advanced tumours. An on-going European multicentre clinical trial, RAPIDO, is investigating the possible benefit of preoperative 5x5 Gy followed by six cycles of capecitabine/oxaliplatin instead of the standard regime with preoperative 1.8 x 25 Gy combined with capecitabine in patients with locally advanced RC⁷⁰. The hypothesis is that the experimental group will have an improved survival and maintained local control.

In summary, based on the results of these trials, an algorithm for neoadjuvant treatment of rectal cancer has been established (*Table 3*)⁷¹. A discussion of implementation of delayed surgery in the intermediate tumour group, as suggested by the Stockholm III study group, is on-going.

Given the potency of RT, there are also many side effects, both acute (erythema, nausea, cystitis, diarrhoea) and long-term (impaired sphincter function, sexual dysfunction, pelvic fractures and ileus)⁷². An increased risk of secondary pelvic malignancies has been suggested, but this could not be seen in a recently published study. In fact, the study showed that men had a decreased risk of prostate cancer after previous RT⁷³. An evaluation of each patient's individual pre-existing condition should always be made before treatment and the final decision is taken at the MDT conference.

Table 3 Radiotherapy recommendations according to tumour classification as described by Blomqvist et al.⁷¹

<u>Favourable "good" tumour</u>	<u>Intermediate "bad" tumour</u>	<u>Advanced "ugly" tumour</u>
Mid/upper rectum ≥ 6 cm T1-T3b	Mid/upper rectum T3c-d	T3 MRF positive
Low rectum ≤ 5 cm T1-T2, T3a	Low rectum T3b-d	T4 with overgrowth to prostate, seminal vesicles, base of urinary bladder, pelvic side wall or floor, sacrum
N0	T4 with peritoneal/vaginal involvement only	Positive lateral lymph nodes
MRF clear	N1-2	
	MRF clear	
↓	↓	↓
Primary surgery	Preop 5x5 Gy with immediate primary surgery	Preop CRT or 5x5 Gy with delayed surgery

1.1.9 Surgical treatment

1.1.9.1 Total mesorectal excision

The technique of total mesorectal excision (TME) was first described by RJ Heald in 1982⁷⁴. Since his presentation of a five-year LRRC rate of 4% in contrast to 25% in a comparable group not operated with TME, several studies have confirmed the good results and the method has been successively implemented throughout the world^{75,76}. TME is today regarded as the gold standard for surgical treatment of RC⁷⁷. The method implies an excision of the rectum and the complete mesorectum in one piece without interruption, including the main supporting blood vessel the inferior mesenteric artery (*Figure 4*). With this method, all regional lymph nodes, including potential tumour growth, are removed, while the important nerve supply of the urethra and the external genitals is spared. TME surgery is primarily warranted for resection of tumours located in the lower or mid rectum. For high rectal tumours, partial mesorectal excision (PME) is sometimes performed instead, but the oncologic safety of this approach is debated^{78,79}. The main advantage of PME is that a higher division of the bowel leaves behind a longer spared part of the healthy rectum entailing a reduced risk of functional side-effects⁸⁰. Originally, TME was performed thorough laparotomy but minimally-invasive techniques have evolved and a large part of rectal resections are today performed by laparoscopy or robot-assisted laparoscopy with similar oncologic results^{81,82}.

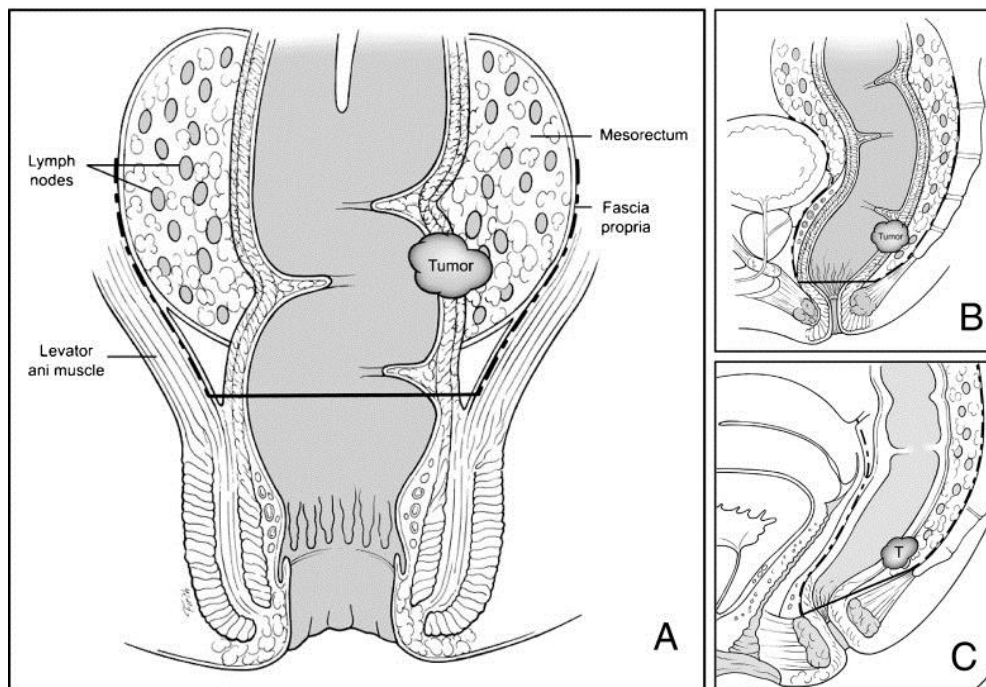


Figure 4⁸³. Appropriate planes for total mesorectal excision. A. Anterior view demonstrating dissection plane between visceral mesorectal fascia and parietal fascia. B. Lateral view of appropriate TME plane in the male. C. Lateral view of TME dissection plane in the female. Reprint with permission.

1.1.9.2 Anterior resection

Anterior resection (AR) is an abdominally performed TME-resection with formation of a direct anastomosis. AR is today the preferred and most commonly used method in RC surgery. The anastomosis may be performed as a straight pairing (end-to-end), a side-to-end junction or as a colon reservoir in shape of a J-pouch. The end-to-end technique has proven to result in worse functional results in terms of bowel continence and urgency, while the side-to-end and J-pouch methods have had equal, superior results^{84,85}. Out of common postoperative surgical complications, the most feared is an anastomotic leak (AL). This occurs in 3-12% of the patients and is associated with increased morbidity and, according to some studies, a worse oncologic outcome^{86,87}. The role of a temporary diverting ileostomy in lowering the risk and consequences of a potential AL has been debated⁸⁸. In a Swedish randomised trial from 2007, RECTODES, 234 patients operated with AR were randomised to either a diverting ileostomy or no stoma and the results indicated a three-fold increased risk of AL in the patients without stoma and an equally elevated risk of reoperation. The results have been confirmed in retrospective studies and construction of a diverting ileostomy in low rectal anastomoses is currently recommended in many centres^{54,89,90}. The benefits and risks of a diverting ileostomy is however still under discussion⁹¹.

1.1.9.3 Abdominoperineal resection

Abdominoperineal resection (APR), also called abdominoperineal excision (APE), is the procedure of choice in low rectal tumours (<6 cm from the anal verge), where a sphincter-preserving surgery cannot be achieved or the functional results are expected to be poor. The original procedure was first described by WE Miles in 1908⁹², but has been slightly modified since then. An APR is initially performed according to a regular TME procedure. When the dissection of the rectum has reached the pelvic floor, the operation is either continued in a supine position or the patient is turned into a prone position and the anus, sphincters and anal canal are excised from below. The specimen is then removed, the perineal defect is closed and an end-colostomy is created. Although Miles' results indicated a reduction of the rate of LRRC, the method is today associated with poorer outcome in terms of local relapse and survival compared with a regular TME with direct anastomosis⁹³⁻⁹⁵.

1.1.9.4 Hartmann's procedure

Hartmann's procedure (HA) is an alternative to AR when the preoperative sphincter function is weak or the patient's general condition would not allow for an AL. The procedure includes a resection of the rectosigmoid colon with closure of the remaining rectal stump. In RC surgery, HA is performed as a TME or PME, but the proximal end of the sigmoid or left colon is led out through the abdominal wall as a stoma. The procedure is associated with high morbidity and mortality rates, possibly due to the population selected for treatment^{49,96}. In an on-going multicentre trial, HAPIRECT, patients with RC where HA is indicated are randomised to either ordinary HA or intersphincteric APR. The hypothesis of the trial is that patients operated with APR will have a lower rate of local complications and a superior quality of life (QoL)⁹⁷.

1.1.9.5 Other types of treatment

For very early rectal tumours, where the risk of spread to regional lymph nodes is small, different techniques for local excision have evolved as an alternative to abdominal surgery^{98,99}. The great advantage with a local excision is a lower risk of complications and functional side effects, and the procedures may be performed in patients for whom abdominal surgery is discouraged. These advantages must of course be weighed against the somewhat elevated risk of recurrence, and a thorough selection of well-informed patients is essential.

An interesting group of patients are those where the neoadjuvant treatment results in a complete tumour remission, with an undetectable tumour at follow-up MRI and clinical investigation. An intensified surveillance according to the so-called Watch-and-Wait regime, has been suggested as an alternative to major abdominal surgery in these selected patients. The results have been promising, indicating a low regrowth rate and survival rates corresponding to those expected for the corresponding stage¹⁰⁰⁻¹⁰².

1.1.10 Classification of residual tumour

The residual tumour classification is an important instrument to evaluate the quality of RC surgery and serves as a complement to the regular postoperative TNM-staging. Resection margin status is given as R0, R1 or R2 and has a crucial impact on the prognosis¹⁰³.

Table 4 Residual tumour classification

Residual tumour	
Rx	Residual tumour cannot be assessed
R0	No residual tumour
R1	Microscopic residual tumour
R2	Macroscopic residual tumour

1.1.11 Adjuvant treatment

The purpose of adjuvant chemotherapy (ChT) is to eliminate potential distant micro-metastases after tumour resection. The treatment has a well-documented effect in CC, but the results are poorer in RC, particularly after performed preoperative RT or CRT^{104,105}. The reasons for this are not fully understood, but a delayed start of the adjuvant treatment due to time-consuming neoadjuvant treatment has been suggested as one explanation¹⁰⁶. The potentially small benefit must be viewed in relation to potentially toxic side-effects of the ChT. Adjuvant ChT is today only recommended in selected cases and should always be preceded by an informative oncologic consultation about the diverging results of a beneficial effect of ChT in RC.

1.1.12 Follow-up

A number of randomised clinical trials have been performed in order to evaluate the potential gains of scheduled follow-up programmes after primary CRC, with varying results¹⁰⁷⁻¹¹⁷. Although the frequency of visits and the type of investigations performed differ widely between studies, there is sufficient evidence of an increased survival to motivate formalised postoperative surveillance^{111,112,115}. The main purpose of the follow-up is to detect early distant spread of the disease, mainly to the liver, and secondly, to diagnose a LRRC at a curable stage. Other profits are early removal of colorectal adenomas, findings of metachronous neoplasms and an improvement of QoL. Due to the different designs and divergent results of previous studies, the intensity of the surveillance is however debated and the economic aspects are not sufficiently evaluated¹¹⁸. An intensified follow-up during the first two years, when a majority of recurrences occur, has been suggested but the evidence for this is still missing. In a recently completed multicentre trial, COLOFOL, 2509 patients radically operated for stage II-III colorectal cancer have been randomised to either low-frequency follow-up (12 and 36 months

after surgery) or high-frequency surveillance (6, 12, 18, 24 and 36 months after surgery). A clinical examination, S-CEA and CT of thorax and liver are performed at each visit¹¹⁹. Final results from the trial will follow shortly. The current recommendation in the Swedish national guidelines for RC corresponds to the low-frequency arm in the COLOFOL trial, with addition of a colonoscopy at 36 months postoperatively⁵⁴. Patients with stage I RC are at low risk of distant tumour recurrence and routine imaging is not recommended, although rectoscopy or colonoscopy is often performed to rule out the emergence of new adenomas¹²⁰.

1.2 LOCAL RECURRENCE

1.2.1 Incidence

The rate of LRRC has decreased considerably during the last decades due to an improvement of several factors in combination. Optimised preoperative staging, the introduction of TME as the preferred surgical method, the addition of preoperative RT to selected patients, an enhanced multidisciplinary management and an implementation of follow-up screening programs have resulted in a decrease in LRRC rates from 20-40% to 5-9%^{66,121-126}. According to the annual report from the SCRCR 2014, five-year follow-up data of patients curatively resected for RC between 1995-2009 showed a decrease in LRRC rate from 13% to 5% during the selected time period¹²⁷ (Figure 5). A majority of LRRCs occur within two years after treatment for primary RC and more than 90% are diagnosed within five years^{128,129}. RT has been shown to increase the disease-free interval and the proportion of LRRC diagnosed after more than two years is higher in these patients^{52,130,131}. About 20-40% of the patients with LRRC have distant metastases already at the time of diagnosis^{126,132}.

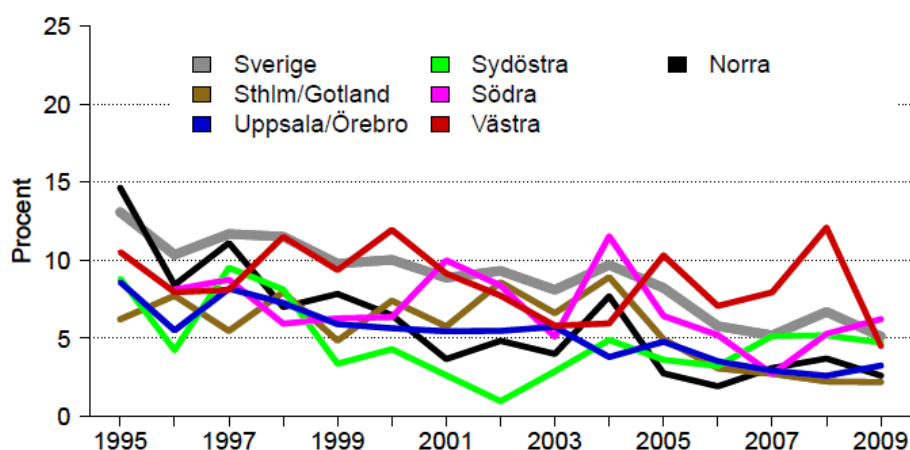


Figure 5 Rate of local recurrence within five years for patients curatively operated for primary rectal cancer 1995-2009, illustrated per region¹²⁷. Reprint with permission.

1.2.2 Risk factors

1.2.2.1 Stage of primary tumour

Despite clear resection margins at primary surgery, several studies have suggested that patients with a stage III primary RC are at higher risk of LRRC than patients with stage I-II tumours^{52,129,133,134}. This may be attributed to the engagement of lymph nodes in stage III tumours, which is already an indication of a dissemination of tumour cells. The risk is even more pronounced in case of perineural or endovascular invasion^{129,134}.

1.2.2.2 Radiotherapy

The beneficial oncologic effects of preoperative RT are indisputable⁶¹. RT not only reduces the rate of LRRC, but also delays the tumour regrowth in those for whom LRRC occurs^{52,130}. Once the LRRC has occurred, a worse survival has been seen in previously irradiated patients, suggesting a more aggressive type of tumour in these patients¹²⁶.

1.2.2.3 Type of primary surgery

LRRC is more common in patients previously operated with APR, compared to those operated with AR⁹³⁻⁹⁵. The reasons for this are probably multifactorial. The anatomy below the termination of the MRF with only a thin layer of tissue surrounding the bowel, may lead to an exposure of the tumour to the CRM and higher rates of positive resection margins¹³⁵. Analyses of bowel specimens after APR have also demonstrated findings of a “waist” at the level of the puborectal muscle, resulting in a more narrow resection margin^{136,137}. The inferior results in this group of patients have led to the suggestion of an alternative surgical technique, where the excisional plane lies outside the external anal sphincter and the levator muscle. There are indications that this Extra-Levator Abdominoperineal Excision (ELAPE) may lead to improved resection margin status and a reduced LRRC rate, but further studies are warranted^{138,139}.

1.2.2.4 Resection margins

A positive CRM is usually pointed out as the most influential risk factor of LRRC¹⁴⁰⁻¹⁴⁴, although some studies have not found any relation^{145,146}. Tumour involvement of the CRM is an important marker of the quality of the surgery and not only increases the risk of LRRC but also implicates a higher risk of distant metastases and a worse survival¹⁴⁷.

1.2.2.5 Complications of surgery

There are divergent results regarding the impact of an AL on the risk of developing a LRRC^{148,149}. In a recent review and meta-analysis, it was found that an AL was associated with an increased risk of LRRC and a poorer both overall and tumour-specific survival⁸⁷. A possible explanation to this effect is a leakage of bacteria causing an infectious environment, stimulating an enhanced proliferation of migrated tumour cells. An increased risk of LRRC has also been reported after perioperative bowel perforation and an explanation of dissemination of cancer cells has been proposed here as well¹³³.

1.2.3 Definition and diagnosis

The definition of LRRC varies in the literature, but according to an international consensus statement, LRRC may be defined as “recurrence, progression or development of new sites of rectal tumour within the pelvis after previous resectional surgery for RC”¹⁵⁰. Tumour growth in the ovaries is usually regarded as metastatic due to a separate vascular supply, unless it is the result of a local overgrowth. A positive tumour biopsy is the first-hand choice for diagnosis, but

radiology with MRI or CT combined with an expertise discussion at an MDT conference may be sufficient when biopsy is not possible¹⁵⁰.

1.2.4 Clinical presentation

The patient may present with a variety of symptoms, depending on the type of previous surgery and involved organ system of the LRRC. Intraluminal tumours in patients with a persistent bowel continuity through the lesser pelvis that present with change of bowel habits or rectal bleeding, are possibly detected earlier than other recurrences. Patients previously treated with APR may have symptoms of micturition disturbance, hematuria, vaginal bleeding, a palpable tumour mass or pain. Pain in the perineum, pelvis or legs is a sign of nerve bundle involvement and has been shown to be an independent marker of a poor prognosis^{151,152}. Other common symptoms are weight loss, fatigue, deep venous thrombosis (DVT) and anaemia. However, a number of patients are asymptomatic and diagnosed during planned follow-up visits¹⁵³.



Figure 6 Local recurrence located in the perineum. (Photo: Torbjörn Holm)

1.2.5 Tumour location

Since an altered anatomy and interrupted surgical planes may prevent clinical staging according to the TNM-system, several anatomical classification models are used in current praxis instead. According to the American Memorial Sloan Kettering classification, the tumour location is categorised in compartments, either axial, anterior, posterior or lateral, where axial tumours are located in the bowel and most often originate from the anastomosis¹⁵⁴ (Figure 7). It is generally assumed that tumours limited to the axial area have the best prognosis and a likelihood of up to 90% R0-resection has been presented in these patients^{154,155}. An anterior location includes tumour growth in the urogenital tract, excluding the ureters, which count as lateral. Tumours in the sacrum, coccyx and presacral area are perceived as posterior and a location close to the pelvic side wall, the ureter, the piriform and obturator internus muscles, the iliac vessels and the

lumbosacral plexus are considered lateral. A disadvantage with this system is that it does not allow for multiple compartment involvement.

According to the Leeds classification, all relapses within the lesser pelvis without contact to bone are named central. The remaining tumours are classified as either sacral or side wall¹⁵⁶ (Figure 8). The Mayo group describes LRRCs as either sacral, anterior, left or right and also involves the extent of fixation¹⁵¹ and Wanebo *et al.* have presented yet another definition which is closely related to the traditional TNM staging system¹⁵⁷. Before the introduction of TME and preoperative RT, central LRRCs used to be the most common, but a change towards a higher proportion of lateral and posteriorly located tumours has been seen in recent years¹⁵⁸. Lateral recurrences are considered to be the greatest surgical challenge and have the least chance of clear surgical resection margins due to the involvement of vital, potentially unresectable structures^{154,159,160}.

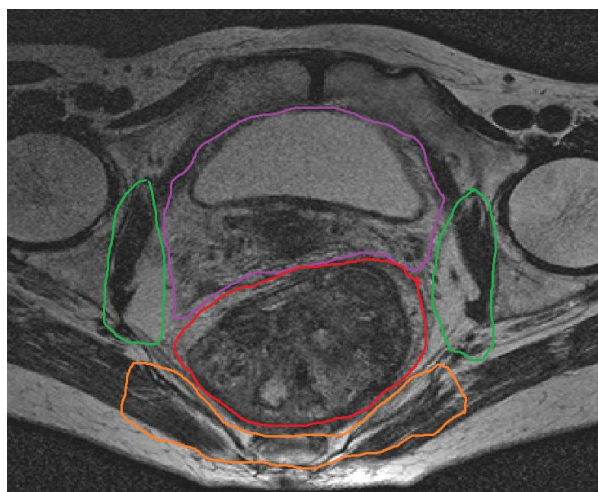


Figure 7 Compartments of the small pelvis according to the Memorial Sloan Kettering classification: axial (red), anterior (purple), posterior (orange) and lateral (green)

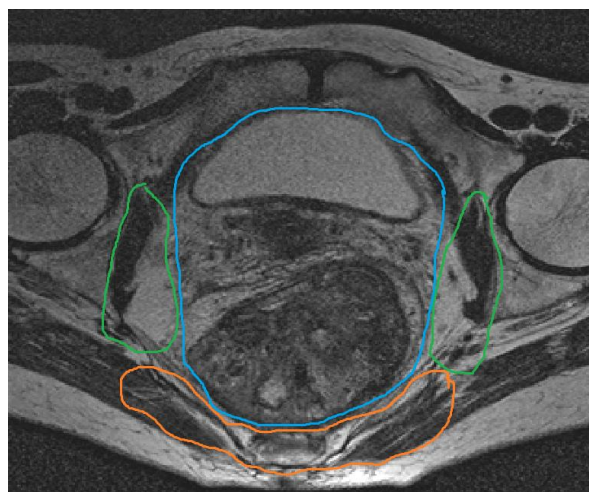


Figure 8 Compartments of the small pelvis according to the Leeds classification: central (blue), sacral (orange) and sidewall (green)

1.2.6 Treatment

1.2.6.1 General considerations

As patients with LRRC constitute a heterogeneous group both regarding location and extension of the tumour, individual conditions must be taken into account and the MDT-conference is of utmost importance^{57,60}. Even a curatively intending treatment may have comprehensive consequences for the patient's future life and an open and informative preoperative consultation is important. Neoadjuvant RT should be recommended to patients who have not yet exceeded the recommended dose^{54,150}. The current Swedish standard fractionation for locally advanced RC is 25-28 x 1.8-2 Gy, but higher doses may be given to patients with LRRC⁵⁴. In cases with

signs of extramural tumour growth, a combined treatment with CRT is normally given. The practice of re-irradiation is controversial¹⁶¹. In a systematic review including 10 previous reports, it was summarised that re-irradiation is feasible, safe and efficient both for patients treated with curative and palliative intent¹⁶². The reported toxicity however seems to increase in surgically treated patients and when the time interval to previously given RT is short^{162,163}.

1.2.6.2 Contraindications for surgery

The absolute contraindications to pelvic resections of LRRC used to be many: peritoneal carcinomatosis, high sacral involvement, growth around the external iliac vessels, invasion of the sciatic nerve, tumour fixation with bony invasion, bilateral hydronephrosis and presence of major leg edema^{164,165}. According to an international consensus statement from the Beyond TME Collaborative Group, led by P Tekkis, in 2013, the only absolute contraindications are today few; bilateral sciatic nerve involvement, circumferential bone involvement and poor performance status or medically unfit patient (*i.e.* severe cardiopulmonary involvement)¹⁵⁰ (Table 5). Among the relative contraindications, it was pointed out that a resection above the S2/3 junction could be performed with suitable surgical expertise and equipment in very dedicated centres and that a predicted R2 resection could be performed in rare circumstances after MDT agreement. The agreement in the consensus group was high (>90%) for all indications except for the indication encasement of external iliac vessels, where it was somewhat lower (78%).

Table 5 Absolute and relative contraindications to surgical resection of local recurrence, according to the Beyond TME Collaborative group¹⁵⁰.

Absolute contraindications	Relative contraindications
Bilateral sciatic nerve involvement	Extension of tumour through the sciatic notch
Circumferential bone involvement	High sacral involvement
Poor performance status/medically unfit patient	Encasement of external iliac vessels – requiring en bloc resection and/or reconstruction of external iliac vessels
	Irresectable distant metastases
	Predicted R2 resection

1.2.6.3 Central recurrences

For axial recurrences limited to the anastomosis or the perineum, an APR of the neorectum is generally the preferred surgical method, while a proximity to or involvement of the genitourinary organs usually require a total pelvic exenteration (PE)¹⁶⁶.

PE was at the time of introduction by A Brunschwig in the late 1940s described as “the most radical surgical attack so far described for pelvic cancer”¹⁶⁷. It was initially performed for palliative purposes only, but as results improved, it has turned into the preferred surgical method for potential cure of advanced pelvic tumour growth^{156,159,167,168}. A varying nomenclature exists, where distinctions of anterior, posterior, supralelevator, total, extended or individualised approaches are found, depending on the compartment(s) resected^{165,169}. A total PE however implies a complete resection of the pelvic viscera, including the rectum, urinary bladder, reproductive organs, pelvic peritoneum and perineum en bloc, with following reconstruction of bowel, perineum and urinary tract^{165,170}.

The procedure is technically demanding and is recommended to be performed only in centres with high operation volumes and an engaged MDT¹⁷¹. In a recent meta-analysis covering 30 studies reporting results after PE for locally advanced RC between 1998-2014, negative resection margins (R0) were reported in 66% (range 32-100%) of the included patients with a LRRC. The overall survival was directly related to margin status, with a nearly three-fold risk of death after R1-resection (HR 2.74, 95% CI 1.29-5.79)¹⁷².

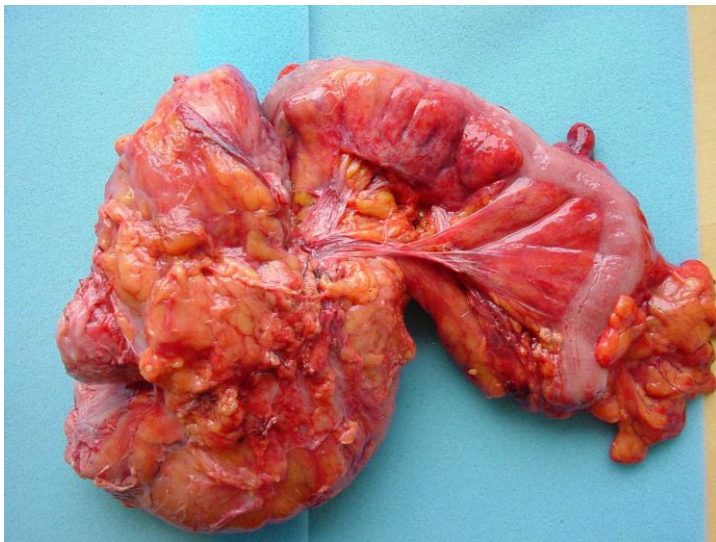


Figure 9 Specimen after en bloc resection of bowel, prostate and urinary bladder (Photo: Torbjörn Holm)

1.2.6.4 Posterior recurrences

Posteriorly and laterally located tumours represent a special challenge in the surgery of LRRC and extended exenterations are sometimes needed in these patients. In a recent review, seven studies of in total 220 patients operated with PE with en bloc sacrectomy were included. R0 resection was achieved in 78% of the patients and a 55% disease-free survival after a median of

33 months of follow-up was seen taken all studies together¹⁷³. All studies were performed in highly dedicated centres. A major problem in this type of surgery is the risk of haemorrhage, due to a rich vascular supply. Sacrectomy is considered to be safe below the S2/S3 junction and pelvic stabilisation is usually not needed. Resections at the S1/S2 level are performed in a few dedicated centres, but this type of surgery entails a higher morbidity, particularly through neurologic impact on urogenital function and pelvic instability¹⁶⁶.

1.2.6.5 Lateral recurrences

Surgery of lateral recurrences is considered to be the most challenging due to potential tumour involvement of large nerves, blood vessels and bony structures. Austin *et al.* have described a method for the resection of tumours with pelvic wall involvement, including resection of the iliac vessels with graft reconstruction¹⁷⁴. With this method, the anatomic plane between the bony pelvis and the sidewall musculature is used for dissection. The authors present a series of 36 performed procedures over a ten-year period. Surgeons from up to five different disciplines participated in the operations and R0 resection margins were achieved in 53% of the patients with no (0%) intraoperative mortality. In another study, reported from Yamada *et al.*, none (0) of the 17 patients that were resected for a lateral LRRC survived five years¹⁶⁰. The lack of larger reported series regarding this type of highly specialised surgery however probably reflects the complexity of the procedure.

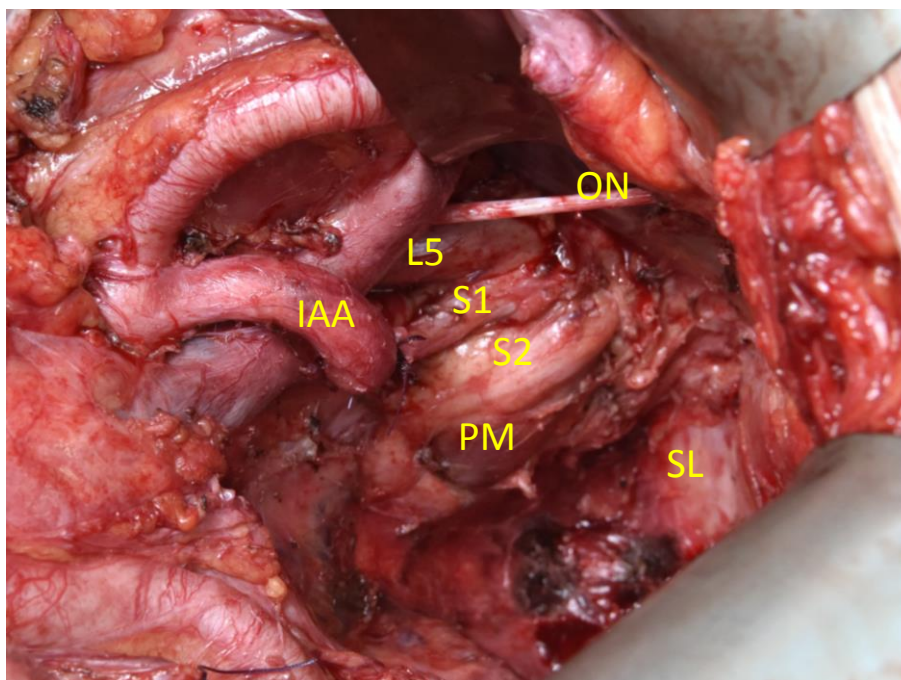


Figure 10 Anatomy after clearance of lateral pelvic wall; ON=obturator nerve, L5-S2=left sacral nerve roots, IAA=internal iliac artery (ligated), PM=piriform muscle, SL=sacrospinal ligament (Photo: Henrik Iversen)

1.2.6.6 Reconstructions

Extensive pelvic resections require reconstructions of bowel, perineum, urinary and genital tracts. Apart from the more obvious construction of a colostomy from the sigmoid colon or an anastomosis re-implanting the urethra into the urinary bladder, more specific procedures may be needed. E Bricker described a technique for reconstruction of the urinary bladder by an ileal conduit¹⁷⁵. The Bricker deviation is today the most widely implemented method for urinary diversion after PE. Continent urinary diversion techniques exist but are generally avoided in these severely ill patients due to higher complication rates¹⁷⁶.

For low extensively growing tumours demanding ELAPE, a larger defect is left in the perineum compared with standard APR¹³⁸. In order to reduce the risk of infections and improve wound healing, a variety of myocutaneous flap procedures have been presented, where the rectus abdominis, the gracilis or the gluteus maximus muscles are harvested from their original sites and rotated into the perineal defect, where they are attached¹⁷⁷⁻¹⁸⁰. Previously presented case series are small, and long-term follow-up data are often missing. Cibula *et al.* presented a study where the results of 16 patients having a rectus abdominis flap after PE were compared with 24 patients having PE without a flap. There was a significantly higher rate of complications (79 vs 44%, $p=0.041$) and worse performance status after six months among the non-flap operated patients¹⁸¹. The largest series was presented by Anderin *et al.*, including 65 patients reconstructed with a gluteus maximus flap after ELAPE. Minor perineal wound infections occurred in 23% of the patients and more severe infections in 18%. However, after 12 months, the gluteal flap was completely healed in 91% of the patients. The authors argue that a gluteus maximus flap has an advantage above the rectus abdominis flap, as the wound is located on a wider distance from the stoma, minimizing the risk of infections¹⁸². New models with biologic mesh implants have been tested and a recent review showed a significant reduction of the perineal hernia rate compared with both gluteal flap surgery and primary closure, but no reduction of the perineal wound infection rate¹⁸³.

1.2.6.7 Intraoperative radiotherapy

The main advantage of intraoperative RT (IORT), in contrast to traditional pre- or postoperative external beam RT, is that it allows for a focused delivery of radiation on a limited target, without risking to include surrounding organs in the radiation field¹⁸⁴. The target is usually a resection area where there is doubt about complete clearance of the tumour. Doses varying between 7.5 and 30 Gy are delivered intra-abdominally during surgery in patients with or without previous RT¹⁸⁵. Peripheral neuropathy is the main toxicity after IORT, reported in 5-14% of the patients in a study from the Mayo Clinic¹⁸⁶. Although invented already in the early 20th century, the first report of modern megavoltage IORT was not published until the early 1980s, presenting a series of 717 Japanese patients treated for various malignancies^{187,188}. Since then, a number of reports of IORT in locally advanced RC or LRRC have been published with varying results¹⁸⁹⁻¹⁹². The main problem of the studies is the lack of randomised controlled trials (RCT) and a wide range of doses and treatment protocols. The only reported randomised trial in the literature included 142 patients with locally advanced RC, who all received neoadjuvant RT, 40 Gy, and then were randomised to either surgical resection only or combined surgical

resection and IORT 18 Gy. After five years, there were no significant differences in LRRC rate, overall survival, disease-specific survival or distant metastases¹⁹³. In Sweden, IORT facilities are available in two centres, Stockholm/Karolinska and Malmö/Lund. Due to the lack of convincing positive study results, the number of treated patients is declining, and IORT is today reserved only for selected cases⁵⁴.

1.2.7 Complications of surgery

Surgery for LRRC has a high risk of complications both in the short and long term and the complication pattern differs depending on the type of surgery performed. Reported early complications following AR or APR are wound infection, wound dehiscence, intraabdominal abscess, AL, ileus, haemorrhage, DVT, pulmonary embolism, cardiac and renal failure and death. In patients operated with APR, perineal wound complications are common and a delayed healing of the perineal wound is reported in up to 24% of the patients^{194,195}. The complication risk is increased after previous RT in both patients treated with AR and APR^{195,196}.

In a review analysis of patients operated with PE, the complication rate varied between 37 and 100% and the median perioperative mortality was 2.2%¹⁹⁷. The complication rate is higher in these patients compared with those with more limited surgical procedures¹⁵⁶. Urinary anastomotic leaks after cystectomy may pose a special problem. Teixeira *et al.* reported a 12% risk of urinary leak and the risk was higher (27%) after resection comprising all four compartments¹⁹⁸. The Clavien-Dindo classification system is often used to quantify complications after surgery, relying on a staging of the severity of each complication according to a four-graded scale¹⁹⁹. Other methods to define complications however also exist. Reported long-term complications are anal incontinence after AR, bowel dysfunction, micturition disorder, sexual dysfunction, fistulas, pelvic fractures and bowel obstructions. The severity is potentiated after previous RT^{200,201}.

1.2.8 Re-recurrence

A re-recurrence may appear after curative surgery for LRRC and reported rates vary between 4-54%²⁰². Most of the patients have also developed distant metastases²⁰³. The actual number of patients who experience a re-recurrence is however small, studies are missing and no specific treatment recommendations exist. A history of multiple pelvic resections infers that a curatively intending treatment only may be applicable under exceptional circumstances.

1.2.9 Distant metastases

Distant metastases constitute a common and feared consequence of CRC, since they are the direct cause of death in a majority of the patients. About 15-25% of the patients have synchronous distant metastases already at the time of primary diagnosis²⁰⁴⁻²⁰⁷ and another 20-

25% will develop metastases during follow-up after curative surgery²⁰⁸⁻²¹¹. The most common metastatic sites are the liver (40-60%) and the lungs (10-20%)²¹¹⁻²¹³, but tumours may also occur in the peritoneum, ovaries, brain, skeleton and lymph nodes^{209,210}.

The view on treatment of distant metastases deriving from CRC has undergone a dramatic change in recent years, especially for liver metastases. From being a definite contraindication to curatively intending surgery, up to 25% of the patients with liver metastases are today treated with metastatic resection, with a reported five-year survival of 30-50%²¹⁴⁻²¹⁷. The patients are routinely discussed at CRC MDT-conferences and preferably also at a specific liver conference. The MRI findings are of major importance for the decision of further treatment. Conversion therapy with ChT is generally given preoperatively in order to shrink the tumour(s) and resection is performed prior to, simultaneously to or after the resection of the primary tumour, depending on patient-related factors, location, type of neoadjuvant treatment and which procedure is expected to be the most complicated²⁰⁷.

In a Danish population-based study by Nordholm-Carstensen *et al.*, 3.8% of the patients with pulmonary CRC metastases underwent metastatic resection, leading to an increased overall survival²¹⁸. The study also reported a significant association between the rate of pulmonary metastases and site of the primary tumour. This has been confirmed in other studies and it appears that RC patients are more prone to get pulmonary metastases than CC patients, possibly due to a different metastatic pathway through extraportal venous drainage of the rectum^{212,218,219}.

1.2.10 Palliative treatment

According to the World Health Organisation (WHO) definition, palliative care is “an approach that improves the quality of life of patients and their families facing the problem associated with life-threatening illness, through the prevention and relief of suffering...”²²⁰. In other words, the contents of a palliative treatment ranges from analgesics or sedatives only to surgical and oncologic tumour-specific measures. In an early, pre-symptomatic stage of the disease, the palliative treatment aims at prolonging life and preventing symptoms, whereas in already symptomatic patients, the goal is to reduce symptoms and improve QoL.

Miner *et al.* performed a prospective analysis of more than 1000 palliative surgical procedures for in all 25 different malignancies. The results revealed an improvement of symptoms in 80% of the patients, but symptoms recurred within less than 2 months in 50% of the patients²²¹. In another study, the same author investigated the results of palliative procedures in 105 patients with LRRC. 23% of the patients were operated with palliative intent due to different symptoms. The largest improvement was seen in patients with obstructive symptoms (70%), followed by bleeding (40%) and pain (20%)²²². Extensive surgical procedures are however discouraged in palliative situations and pelvic exenteration is generally contraindicated²²³.

RT has well-documented analgesic effects against symptoms deriving from bone metastases^{224,225}. Regarding intrapelvic recurrences, RT may reduce both local symptoms of

pain, obstruction and bleeding and the treatment is recommended for palliative treatment of RC in the Swedish national guidelines⁵⁴. ChT is normally recommended at an asymptomatic, life-prolonging stage, since the patient's general condition must not be too marked by the disease. Ito *et al.* however evaluated the effect of CRT versus RT alone on pain in patients with LRRC and found a significantly longer duration of pain relief ($p=0.019$) in patients treated with CRT (median 7.8 months) compared with RT (median 4.0 months) and a significantly prolonged survival ($p=0.046$)²²⁶. CRT may be relevant under certain circumstances, particularly when a curatively intending treatment has not been entirely ruled out.

1.2.11 Survival

Survival data after curatively intending treatment of LRRC vary widely between studies. A variety of factors, including tumour location, type of surgery, resection margins and presence or absence of distant metastases may affect the results. A report from five pelvic recurrence specialist institutions including 533 LRRC patients treated with tumour resection, revealed a 28% five-year overall survival and a 37% cancer-specific survival for all included patients and 44% five-year survival for R0 resected patients²⁰³. However, more than 50% of the included patients had a posterior or a lateral location of the LRRC. In contrast, a Norwegian population-based study including all patients with diagnosed LRRC in Norway reported five-year survival rates of 55% for R0 resected patients, but the corresponding value for all patients was low, only 15%²²⁷. From other studies, five-year survival rates of up to 70% have been reported after R0 resection and a rate below 10% disregarding treatment or not^{124,228-232}. A curative resection is the only chance for tumour-free survival in patients with LRRC.

1.2.12 Quality of life

An increasing interest for QoL aspects in patients with LRRC has evolved with the improvement of surgical techniques. Considering the poor diagnosis and high morbidity risk of extensive surgery, it is obvious that many aspects of life will be affected.

There are several tests to quantify QoL aspects, of which EORTC-QLQ C30, FACT-C and SF-36 are the most commonly used²³³⁻²³⁵. All studies evaluate physical, emotional, social and cognitive functioning in different ways and the two latter also evaluate symptoms. In one of the first studies reporting QoL in patients with LRRC, patients with a manifest LRRC were compared with matched patients without evidence of recurrence. The study showed that the QoL scores were significantly lower among the LRRC patients regarding all aspects from emotional, physical and social functions to gastrointestinal problems, insomnia and appetite²³⁶. Several studies have however shown an increasing QoL after curative resection of the LRRC, but unchanged or even worse values if a complete tumour resection is not achieved²³⁷⁻²⁴⁰.

2 AIMS OF THE THESIS

Overall aim

The overall aim of the thesis was to gain more knowledge about the characteristics, management and outcome of patients with LRRC in Sweden.

Specific aims

Paper I

To investigate whether the time interval between primary surgery for RC and the time of diagnosis of LRRC had any impact on survival after the LRRC diagnosis

Paper II

To assess whether factors related to the patient, the primary tumour or the LRRC may predict treatment intention with curative or palliative intent

Paper III

To investigate potential differences in treatment intention in relation to geographical region or time period and to assess outcome and prognosis in patients with LRRC

Paper IV

To evaluate surgical treatment of patients with LRRC treated with and without tumour resection and to explore complications and prognosis after surgery

3 PATIENTS AND METHODS

3.1 PAPER I

3.1.1 Study population

All patients operated with surgically radical (R0-R1) abdominal surgery for primary RC between January 1st 1995 and December 31st 2002 and with a reported diagnosis of LRRC to the SCRCR were identified in the registry. Patients with reported distant metastases prior to or simultaneously to the date of diagnosis of LRRC were excluded. Access of data was made on March 23rd 2010.

3.1.2 Method – data collection

Identification of the patients was made through the personal identification number that is unique for each Swedish citizen. Information about the patient (sex, age), characteristics and treatment of the primary tumour (T-stage, N-stage, Dukes' stage, tumour height, RT, type of primary surgery, date of LRRC diagnosis and follow-up data, including death date and date of last follow-up) were extracted and processed. Data concerning resection of the LRRC were not available in the registry and information concerning this variable was accessed from medical records that were collected from the hospitals concerned (see further description of the process in the method section for paper II-IV).

The time from date of primary surgery for RC to date of diagnosis of the LRRC was calculated and the patients were divided into two groups; those with an early LRRC (ELR), diagnosed <12 months after primary surgery and those with a late LRRC (LLR), diagnosed ≥ 12 months after primary surgery.

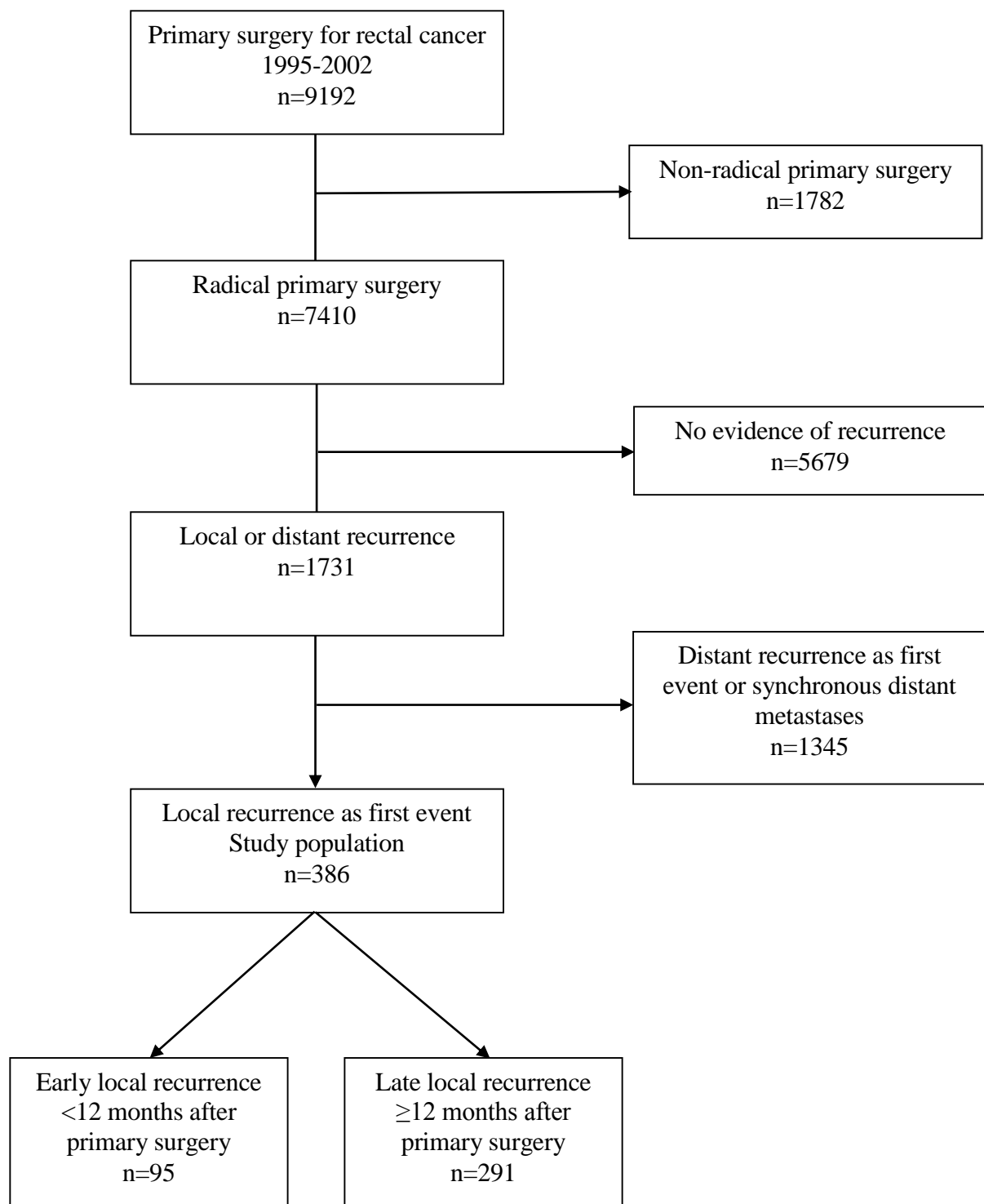
3.1.3 Statistics

Statistical analyses were performed using Stata®12 (StataCorp, TX, USA). The relationship between the dichotomised variable time to local recurrence and categorical variables (sex, type of surgery, RT) was tested using the chi-square test of independence, while the relationship with ordinal variables (age, tumour height, stage) was tested using the chi-square test for trend. When analysing time as a continuous variable as in difference in time to LRRC in irradiated and non-irradiated patients, the Mann-Whitney test was used.

In the survival analysis, end of follow-up was set to April 30th, 2009. Survival was estimated using the Kaplan-Meier method and the effect of clinical variables on risk of death was calculated with Cox proportional hazards regression. The results of the Cox regression analysis were presented as Hazard ratios (HR), where the risk of death for each value of a variable was

compared with the reference value of the same variable. Each HR-value was complemented with a 95% confidence interval (CI) and a p-value calculated with Wald's test. A stepwise selection procedure using backward elimination was applied to identify the clinical variables with the strongest independence. All factors were included in the stepwise model and the replication stability was assessed with a bootstrap resampling procedure, as proposed by Sauerbrei et al²⁴¹.

Figure 11 Flow-chart of the selection of patients of study I



3.2 PAPER II-IV

3.2.1 Study population

In similarity with paper I, all patients abdominally operated for primary RC between January 1st 1995 and December 31st 2002 and with a diagnosis of LRRC reported to the SCRCR were eligible. In contrast to paper I, no selection based on outcome of the primary surgery was made on this stage and patients with a diagnosis of distant metastases within 3 months before diagnosis of the LRRC were also included in the registry output. In total, 730 patients fulfilling the inclusion criteria mentioned above were identified in the SCRCR and a data output on these patients was created on March 23rd 2010.

3.2.2 Method – data collection

Medical records covering the time from primary surgery of RC to date of last visit after treatment of LRRC were collected from the 76 different Swedish hospitals responsible for the 730 identified patients. During the main part of the time studied, the hospitals did not have computerised systems for medical records and most of them were kept in archives. Letters were sent to both the head of the surgical department of each hospital and to the archives where the medical records were held, asking for permission and help with copying and shipping of the material. All hospitals agreed to share their medical records. Three hospitals in the Stockholm region (Karolinska University Hospital, Danderyd hospital and Ersta hospital) were visited and the collection of data was made on site. All collection, reading and interpretation of the medical records was made by the author of this thesis.

The medical records were studied according to a specific protocol, where both information already reported to the registry, such as patient and primary tumour data, and “new” information concerning the LRRC, was noted. Regarding the patient and primary tumour, information about date of birth, sex, hospital, tumour height, neoadjuvant treatment, type of surgery, resection margin, pathological TNM-stage, Dukes’ stage, adjuvant treatment and postoperative complications was collected. Furthermore, information about the LRRC concerning symptoms, diagnosis, preoperative assessment, discussion at MDT conference, treatment intention, neoadjuvant treatment, type of surgical treatment, early and late postoperative complications, resection margins, type of palliative treatment, presence and type of distant metastases, re-recurrence and follow-up data was compiled. The information was inserted in a data file that was merged with the registry output file, keeping all variables from both the registry and the medical records intact in the same file. From this point, all used data were taken from variables based on information from the medical records, apart from date of diagnosis of the LRRC and date of death, which was taken from the registry.

Medical records of 32 patients could not be found or lacked essential information. After putting the file together, some exclusions of patients were made. Patients with a diagnosis of distant metastases before or simultaneously to the LRRC, patients with a surgically non-radical (R2) primary surgery and patients without radiology or pathology confirming the diagnosis of LRRC

were excluded. Other reasons for exclusion included local excision or unclear resection margins at primary surgery, primary surgery outside the time interval 1995-2002, tumour level above 15 cm and anal cancer. After exclusion, 426 patients remained and they constituted the study cohort in paper II, III and IV (*Figure 12*).

Figure 12 Flow-chart of the selection of patients of study II-IV, step 1

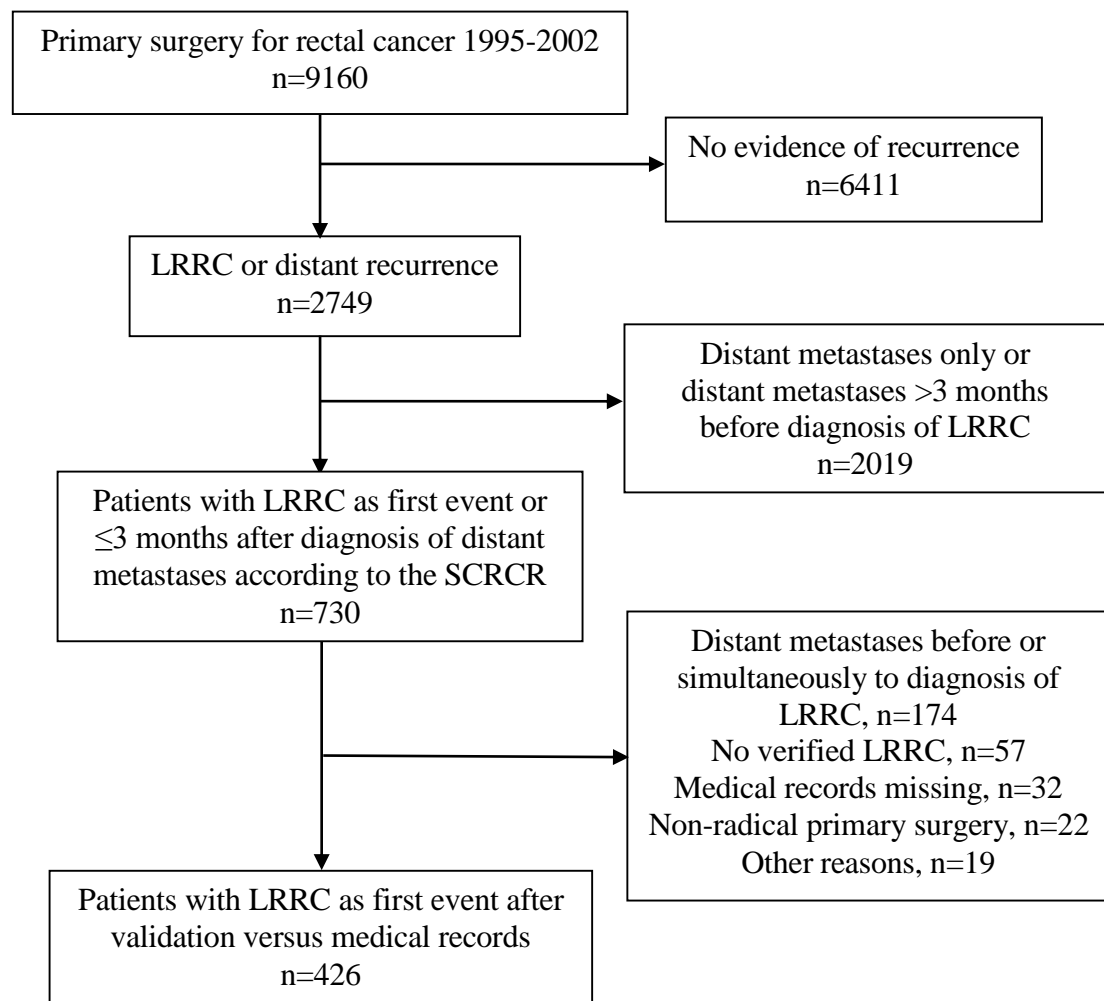
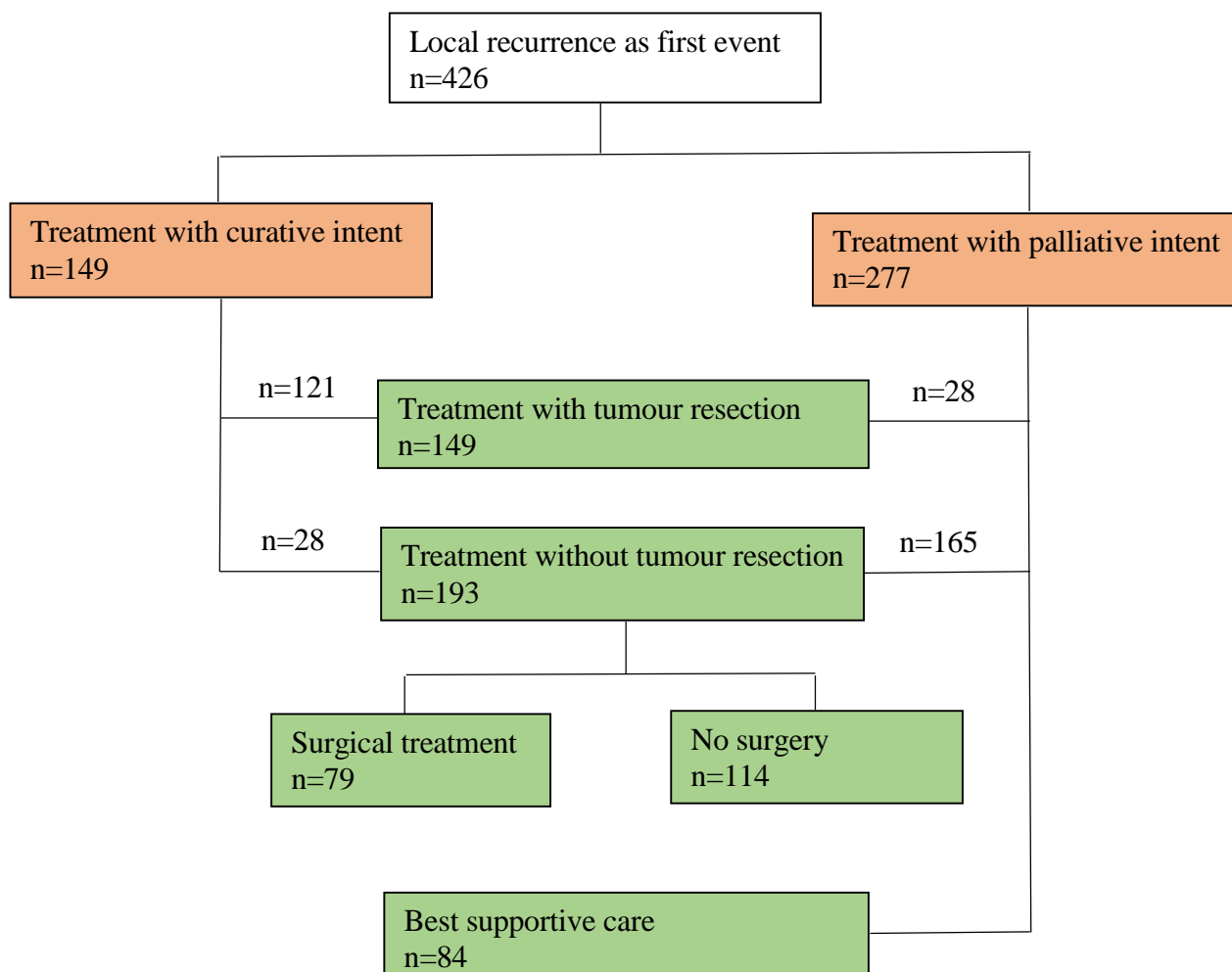


Figure 13 Flow-chart of the selection of patients of study II-IV, step 2. Brown colour represents groups used in paper II and III. Green colour represents groups used in paper IV.



3.2.3 Method – definitions

The definition of LRRC used in the studies was a regrowth of tumour in the lesser pelvis after previous radical (R0-R1) abdominal surgery for primary RC and a diagnosis of LRRC reported to the SCRCR. The diagnosis should have been stated by a radiologist or a pathologist. Indirect findings of a LRRC, such as a hydronephrosis, were not sufficient for diagnosis. Tumour growth in the ovaries was regarded as metastatic unless it was the result of direct overgrowth.

The location of the LRRC was defined as axial, anterior, posterior or lateral, according to the Memorial Sloan-Kettering classification¹⁵⁴. Axial tumours included a location at the anastomotic site or in the perineum, anterior tumours were located in the internal genitals (uterus, vagina, prostate, seminal vesicles) or the anterior urinary tract (urinary bladder, urethra), posterior tumours had a location in the sacrum, coccyx or the presacral region, while

lateral tumours were located in the lateral pelvic wall, ureter, internal obturator muscle, iliac vessels and lumbosacral plexus. The different sites were thereafter grouped into two compartments, with central recurrences, including those with an axial and/or anterior involvement only in one and posterolateral recurrences, including those with a posterior and/or lateral involvement only in another group. Tumours with involvement of both central and posterolateral compartments were named multifocal and tumours in which the location could not be determined were named unspecified. All tumours with posterolateral, multifocal or unspecified location were thereafter named non-central.

Co-morbidity was defined as a documented diagnosis of cardiovascular disease (hypertonia, ischemic heart disease, heart failure, atrial fibrillation, stroke), neurologic disease (dementia, depression, psychosis), respiratory disease (asthma, chronic obstructive pulmonary disease), diabetes, previous or synchronous cancer other than rectal cancer or other conditions (renal failure, liver failure, HIV, hepatitis) at time of diagnosis of LRRC.

Postoperative complications were documented according to diagnosis in the medical records. No rating of the severity of the conditions was made.

The administration of Swedish cancer care is organised in six geographical regions, with one University Hospital per region. All regions follow the same national treatment programme, but with different implementations according to the structure and resources of each region. For the analyses in paper III, the regions were randomly named region 1, 2, 3, 4, 5 and 6.

3.2.4 Method – analysed groups

3.2.4.1 Paper II

In paper II, the patients were divided into two groups, based on the initial treatment intention of the LRRC. 149 patients were treated with curative intent and the remaining 277 patients, consisting of both patients treated with oncologic palliative treatment and those only receiving best supportive care (BSC), were put together in a group named treatment with palliative intent (*Figure 13*).

3.2.4.2 Paper III

In paper III, the patients were analysed according to treatment intention, as described in paper II, region and time period. Resection margin status was analysed for patients treated with tumour resection with curative intent. In two of the analyses, the patients were analysed according to the geographical region where they had been assessed for their LRRC.

For the analysis of changes over time, the material was divided into three time periods that were comparable in length, based on the year of diagnosis of the LRRC. The periods were set to: period 1: 1995-1998, period 2: 1999-2002 and period 3: 2003-2007.

3.2.4.3 Paper IV

In this study, the patients were analysed according to the type of performed treatment of the LRRC. Patients where a surgical resection of the LRRC had been performed, disregarding treatment intention, were analysed as the “treatment with tumour resection” group, while patients receiving surgical or oncologic treatment, disregarding treatment intention, but where tumor resection had not been performed, were analysed as the “treatment without tumour resection” group. The patients who had not received any specific surgical or oncologic treatment were analysed as the “best supportive care” group (*Figure 13*). A tumour resection was defined as a removal of all or part of the LRRC, either by an abdominal or a local resection procedure.

3.2.5 Statistics

3.2.5.1 Paper II

As for paper I, the statistical analyses in paper II, III and IV were carried out using Stata® 12 (StataCorp, TX, USA). All statistical tests were two-sided and statistical significance was set at $\alpha=0.05$ in all papers. Logistic regression was used to calculate the association between clinical factors and treatment intention and the results were expressed as Odds Ratios (OR) for treatment with palliative intent compared with treatment with curative intent, complemented with a 95% CI. P-values were calculated with Wald’s test. Survival was calculated from time of diagnosis of the LRRC to date of death or date of last recorded follow-up. Median follow-up time was calculated with the reversed Kaplan-Meier method as described by Schemper and Smith²⁴². The Kaplan-Meier method was used to graphically illustrate survival for patients treated with curative and palliative intent and to illustrate survival according to time to local recurrence, age, presence of symptoms, hydronephrosis and LRRC location in patients treated with curative intent. Differences in survival were tested using the log-rank test. The Cox regression model was used to estimate HR of death by any cause and was supplemented with a 95% CI. The proportionality of the Hazard functions was visually inspected and tested with Shoenfeld’s residuals²⁴³.

3.2.5.2 Paper III

In this study, logistic regression was used to assess the association of time period of diagnosis of LRRC and geographical region to treatment intention. The results were expressed as unadjusted and adjusted (for age at diagnosis, sex and LRRC location) ORs for treatment with curative intent. Unadjusted logistic regression was also performed for estimation of the association between time period, region and location to resection margins and given values represent the OR for a non-radical (R1/R2) resection. As in paper II, the Cox proportional Hazards regression was used to estimate risk of failure, in this study including re-recurrence, distant metastases or death by any cause. Cumulative incidence functions were used to graphically illustrate failure patterns, estimating the probability of re-recurrence, distant metastases or death as first failure. Time to failure was calculated from date of surgery of the LRRC.

3.2.5.3 *Paper IV*

A chi²-test was used to assess the association between clinical variables and performed treatment with tumour resection, treatment without tumour resection or best supportive care. The results were expressed as p-values. Kaplan-Meier plots were used to illustrate overall survival for the four different treatment groups (curative resection, non-curative resection, treatment without resection and BSC) and differences in survival were tested with the log-rank test. The same methods were applied to illustrate survival in resected patients with or without complications.

4 RESULTS

4.1 PAPER I

4.1.1 Patient and primary tumour characteristics

According to data from the SCRCR, 9192 patients were abdominally resected for primary RC during the period 1995-2002. Of these, 386 patients had a diagnosis of LRRC as first and isolated event reported to the registry. Median follow-up time for all patients was 8.6 (range 2.1-13.8) years from date of primary surgery. The median time to local recurrence was 1.7 (range 0.1-7.9) years.

4.1.2 Early and late local recurrence

In all, 95 patients (25%) had an ELR and 291 patients (75%) had an LLR. There were no significant differences between the groups regarding age, sex, tumour height or type of primary surgery (*Table 6*). Tumour stage was significantly associated with time to LRRC in a test for trend, with a higher proportion of stage III tumours and a lower proportion of stage I tumours in the ELR group compared with the LLR group. This difference remained in a multivariable analysis with a close to three-fold increased risk of an ELR among stage III tumours (OR 2.74, 95% CI: 1.1-7.0). Previous RT was significantly more common in the LLR group, both in uni- and multivariable analyses. The median time to LRRC was 2.0 years among the irradiated patients and 1.5 years among patients treated with surgery alone ($p=0.004$) (*Figure 14*). There was no significant difference in the proportion of patients treated with tumour resection for their LRRC between the groups ELR and LLR (38% vs 32%, $p=0.35$).

4.1.3 Survival

Median survival was 1.2 years for all patients, 1.1 years for ELR patients and 1.3 years for LLR patients. The difference in survival between patients with ELR and LLR was not significant ($p=0.53$) (*Figure 15*). Factors with a significant influence on survival in both uni- and multivariable analyses were age at diagnosis of the LRRC, stage of the primary tumour and performed resection of the LRRC. Patients with a stage III primary tumour had a worse prognosis than patients with a stage I-II tumour (HR 1.3, 95% CI: 1.0-1.6). Age and resection of the LRRC were the most important prognostic factors in the study, where older patients had a worse survival (HR 1.9, 95% CI: 1.3-2.7) and resected patients had a better survival (HR 0.4, 95% CI: 0.3-0.5) in a stepwise model. In an additional analysis, a stratification on the variable resection of the LRRC was performed. In resected patients, the risk of death was increased in patients with stage III primary tumour (HR 1.6, 95% CI: 1.1-2.4) previously performed APR (HR 1.9, 95% CI: 1.2-3.0) or HA (HR 2.2, 95% CI: 1.1-4.4). On the contrary, in patients without

resection of their LRRC, age and sex were the only factors with significant influence on survival. Older patients (≥ 80 years) had an increased risk of death compared with younger (HR 1.0, 95% CI:1.2-3.0) and female patients had a decreased risk of death compared with male (HR 0.7, 95% CI:0.5-1.0) in a stepwise model. Time to local recurrence had no prognostic influence in neither resected nor non-resected patients.

Table 6 Patient and primary tumour characteristics in patients with early and late LRRC.

	Early local recurrence <12 months (n=95)	Late local recurrence ≥ 12 months (n=291)	P-value ^{†,‡}
Age^a, years			
<60	21 (22)	39 (13)	0.20 [‡]
60-69	25 (26)	78 (27)	
70-79	28 (30)	105 (36)	
≥ 80	21 (22)	69 (24)	
Median age, [min-max]	71 [32-90]	72 [31-91]	
Sex			
Male	61 (64)	160 (55)	0.12
Female	34 (36)	131 (45)	
Primary tumour			
Tumour height			
0-5 cm	24 (25)	112 (39)	0.16 [‡]
6-10 cm	43 (45)	95 (33)	
11-15 cm	26 (27)	78 (27)	
Missing	2 (2)	6 (2)	
Stage			
I	7 (7)	47 (16)	0.023 [‡]
II	31 (33)	103 (35)	
III	56 (59)	139 (48)	
Missing	1 (1)	2 (1)	
Type of surgery			
AR	58 (61)	164 (56)	0.52
APR	25 (26)	95 (33)	
HA	12 (13)	32 (11)	
Radiotherapy			
No	58 (61)	139 (48)	0.029
Yes	33 (35)	138 (47)	
Missing	4 (4)	20 (6)	

^aAge at operation of primary tumour. [†]Chi-square test of independence. [‡]Chi-square test for trend. [#]Missing data not included in test.

Figure 14 Time to local recurrence in non-irradiated and irradiated patients

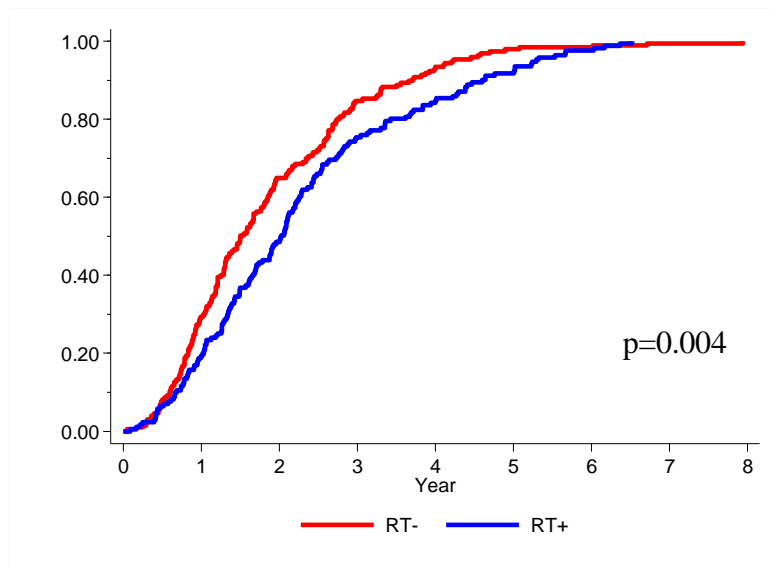
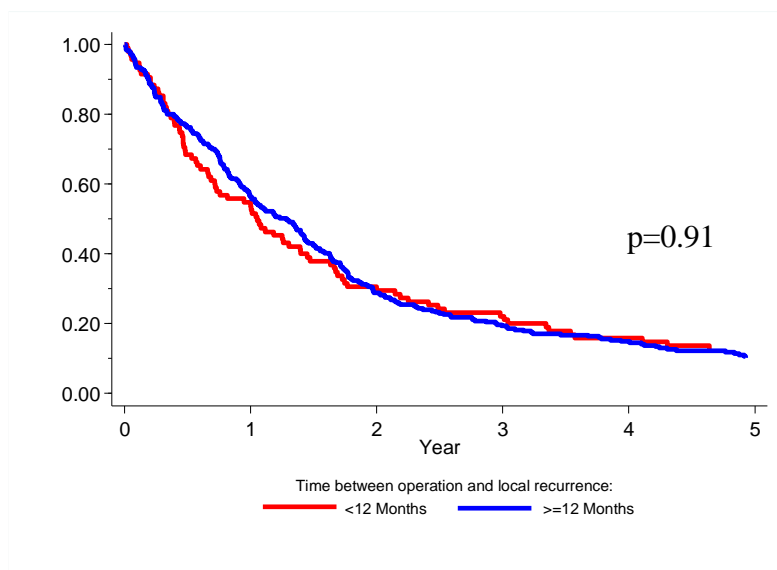


Figure 15 Overall survival in patients with early and late local recurrence



4.2 PAPER II

4.2.1 Patient, primary tumour and LRRC characteristics

Characteristics of all included patients are presented in *Table 7* and *8*. Median time from primary surgery to diagnosis of LRRC was 1.7 (range 0.05-7.9) years and median age at the time of diagnosis of LRRC was 74 (range 31-93) years. A majority of the patients (50.9%) had been operated with anterior resection (AR) at the time of primary surgery and a majority of the patients (55.6%) had stage III primary tumours. In all, 325 patients (76.3%) were operated with clear resection margins (R0) at primary surgery.

Symptoms were present in 360 (84.5%) of the patients at time of diagnosis of LRRC. The most common symptom was pain, present in 130 (30.5%) of the patients, followed by anal or perianal symptoms (103 patients), change of bowel habits (77 patients), urogenital symptoms (67 patients), reduced general condition (30 patients), a palpable tumour (24 patients), and lower limb symptoms (16 patients). Regarding location of the LRRC, it was classified as central in 213 patients (50.0%), of which it was axial only in 150 patients, anterior only in 29 patients and 34 patients had a combination of the two locations. Another 65 patients (15.3%) had a posterolateral location, where the LRRC was posterior only in 41 patients, lateral only in 16 and 8 patients had a combined posterolateral location. 123 patients (28.9%) had a combination of central and posterolateral locations and in 25 patients (5.9%), the tumour location was not specified.

4.2.2 Predictors of treatment intention

In all, 149 patients (35.0%) received treatment with curative intent and 277 patients (65.0%) were treated with palliative intent. Regarding primary tumour related factors, the risk of treatment with palliative intent was significantly increased in patients aged ≥ 80 years at time of primary surgery (OR 3.59, 95% CI: 1.73-7.45), after a performed APR at primary surgery (OR 5.16, 95% CI: 2.97-8.97) or a performed HA (OR 2.81, 95% CI: 1.40-5.60) or a stage III primary tumour (OR 3.43, 95% CI: 1.75-6.72). Investigated factors without association to treatment intention were sex, tumour height, neoadjuvant treatment, pT-stage, postoperative complications, reoperation within 30 days and margin status. Tumour height, T-stage and margin status had a significant association to treatment intention in a univariable analysis, but not in the multivariable analysis.

Regarding factors related to the LRRC, age ≥ 80 years at time of diagnosis (OR 4.82, 95% CI: 2.37-9.80) was the factor that most significantly increased the risk of treatment with palliative intent (*Table 9*). Presence of symptoms (OR 2.79, 95% CI: 1.56-5.01), presence of hydronephrosis (OR 1.95, 95% CI: 1.06-3.58) and a non-central location of the LRRC (OR 1.79, 95% CI: 1.15-2.79) were also associated with a higher probability of treatment with palliative intent. Co-morbidity had no association to treatment intention.

Table 7 Patient and primary tumour characteristics of all patients included in study II-IV

	All patients n=426
Sex	
Male	231 (54.2)
Female	195 (45.8)
Age†	
<60	71 (16.7)
60-69	115 (27.0)
70-79	141 (33.1)
≥80	99 (23.2)
Median (range)	72 (27-92)
Tumour height	
High (11-15 cm)	109 (25.6)
Medium (6-10cm)	152 (35.7)
Low (0-5 cm)	156 (36.6)
Data missing	9 (2.1)
Neoadjuvant treatment	
No trt	263 (61.7)
(C)RT	162 (38.0)
Data missing	1 (0.2)
Type of surgery	
LAR	217 (50.9)
APR	144 (33.8)
Hartmann's proc	65 (15.2)
(y)pT-stage	
T1-T2	81 (19.0)
T3-T4	334 (78.4)
Data missing	11 (2.6)
Stage	
I	55 (12.9)
II	128 (30.0)
III	237 (55.6)
Data missing	6 (1.4)
Post-operative complication	
No	239 (56.1)
Yes	181 (42.5)
Data missing	6 (1.4)
Re-operation within 30 days	
No	380 (89.2)
Yes	42 (9.9)
Data missing	4 (0.9)
Margin status of primary surgery	
R0	325 (76.3)
R1	101 (23.7)

Table 8 Local recurrence characteristics of all patients included in study II-IV

	All patients n=426
Age	
<60	59 (13.8)
60-69	98 (23.0)
70-79	138 (32.4)
≥80	131 (30.8)
Median age (range)	74 (31-93)
Time to LRRC	
<12 months	112 (26.3)
≥12 months	314 (73.7)
Median months (range)	20 (1-95)
Symptoms at diagnosis	
No	61 (14.3)
Yes	360 (84.5)
Type of symptom	
Pain	130 (30.5)
Anal/perianal symptom	103 (24.2)
Change of bowel habits	77 (18.1)
Urogenital symptom	67 (15.7)
Reduced general cond.	30 (7.0)
Palpable tumour	24 (5.6)
Lower limb symptom	16 (3.8)
Hydronephrosis	
No	348 (81.7)
Yes	78 (18.3)
Location of LRRC	
Central	213 (50.0)
Non-central	213 (50.0)
Co-morbidity#	
No	165 (38.7)
Yes	261 (61.3)
Type of co-morbidity	
Cardiovascular disease	183 (43.0)
Diabetes	44 (10.3)
Previous other cancer	29 (6.8)
Synchronous cancer	37 (8.7)
Asthma/COPD	28 (6.6)
Neurological disease	19 (4.5)
Other	23 (5.4)

Table 9 Local recurrence related factors with significant association with treatment intention, n=426

Variable	Treatment with curative intent, n=149	Treatment with palliative intent, n=277	Multivariable OR (95% CI)	Multivariable p-value
Age				
<60	32 (21.5)	27 (9.7)	ref	
60-69	42 (28.2)	56 (20.2)	2.09 (1.04-4.20)	
70-79	41 (27.5)	97 (35.0)	3.62 (1.84-7.13)	
≥80	34 (22.8)	97 (35.0)	4.82 (2.37-9.80)	<0.001
Time to LRRC				
<12 months	44 (29.5)	68 (24.5)		
≥12 months	105 (70.5)	209 (75.5)		
Symptoms at diagnosis				
No	36 (24.2)	25 (9.0)	ref	
Yes	111 (74.5)	249 (89.9)	2.79 (1.56-5.01)	0.001
Type of symptom				
Pain	32 (21.5)	98 (35.4)		
Anal/perianal symptom	37 (24.8)	66 (23.8)		
Change of bowel habits	27 (18.1)	50 (18.1)		
Urogenital symptom	18 (12.1)	49 (17.7)		
Reduced general cond.	7 (4.7)	23 (8.3)		
Palpable tumour	12 (8.1)	12 (4.3)		
Lower limb symptom	1 (0.7)	15 (5.4)		
Hydronephrosis				
No	129 (86.6)	219 (79.1)	ref	
Yes	20 (13.4)	58 (20.9)	1.95 (1.06-3.58)	0.031
Location of LRRC				
Central	89 (59.7)	124 (44.8)	ref	
Non-central	60 (40.3)	153 (55.2)	1.79 (1.15-2.79)	0.009

4.2.3 Follow-up and survival

Median follow-up time was 8.6 (range 2.0-12.3) years and median survival from date of diagnosis of the LRRC was 1.1 (0-12.3) years. Overall five-year survival was 23.1% for patients treated with curative intent and 1.0% for patients treated with palliative intent (logrank $p < 0.001$) (*Figure 16*). The five-year survival was 8.9% for all patients. A Cox regression analysis of patients treated with curative intent, revealed that the same LRRC related factors that influenced the selection for treatment intention also affected the risk of death, including age ≥ 80 years (HR 2.44, 95% CI: 1.55-3.86), stage III primary tumour (HR 1.83, 95% CI: 1.25-2.68), presence of symptoms (HR 1.92, 95% CI: 1.20-3.05), non-central location (HR 1.51, 95% CI: 1.01-2.26) and presence of hydronephrosis (HR 2.02, 95% CI: 1.18-3.44). These results were valid for both univariable and multivariable analysis. *Figure 17* represents Kaplan-Meier illustrations of overall survival according to the factors of significant influence for survival in patients treated with curative intent.

Figure 16 Survival of patients treated with curative and palliative intent, n=426

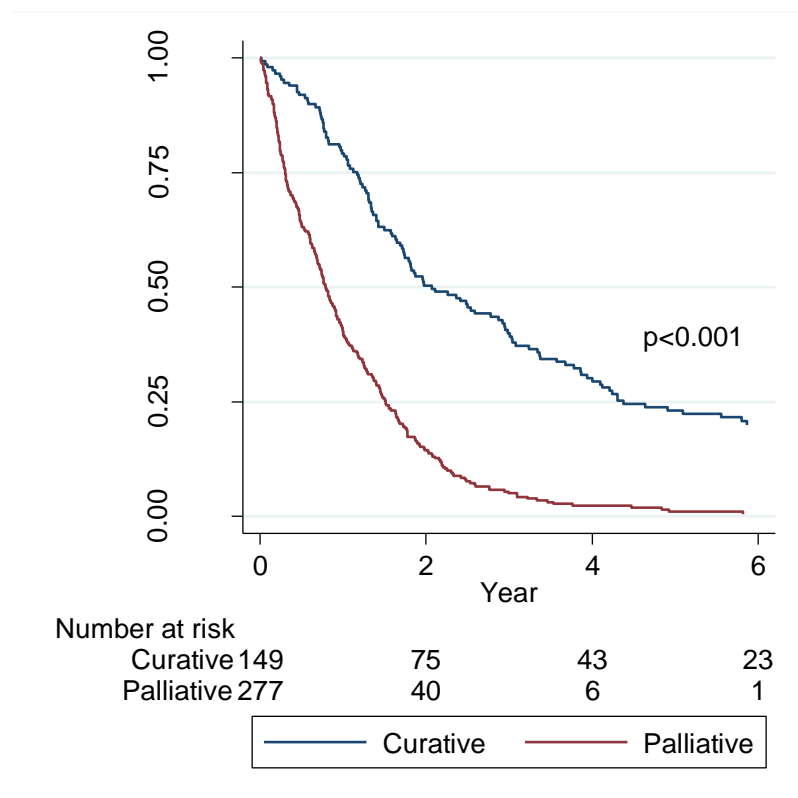
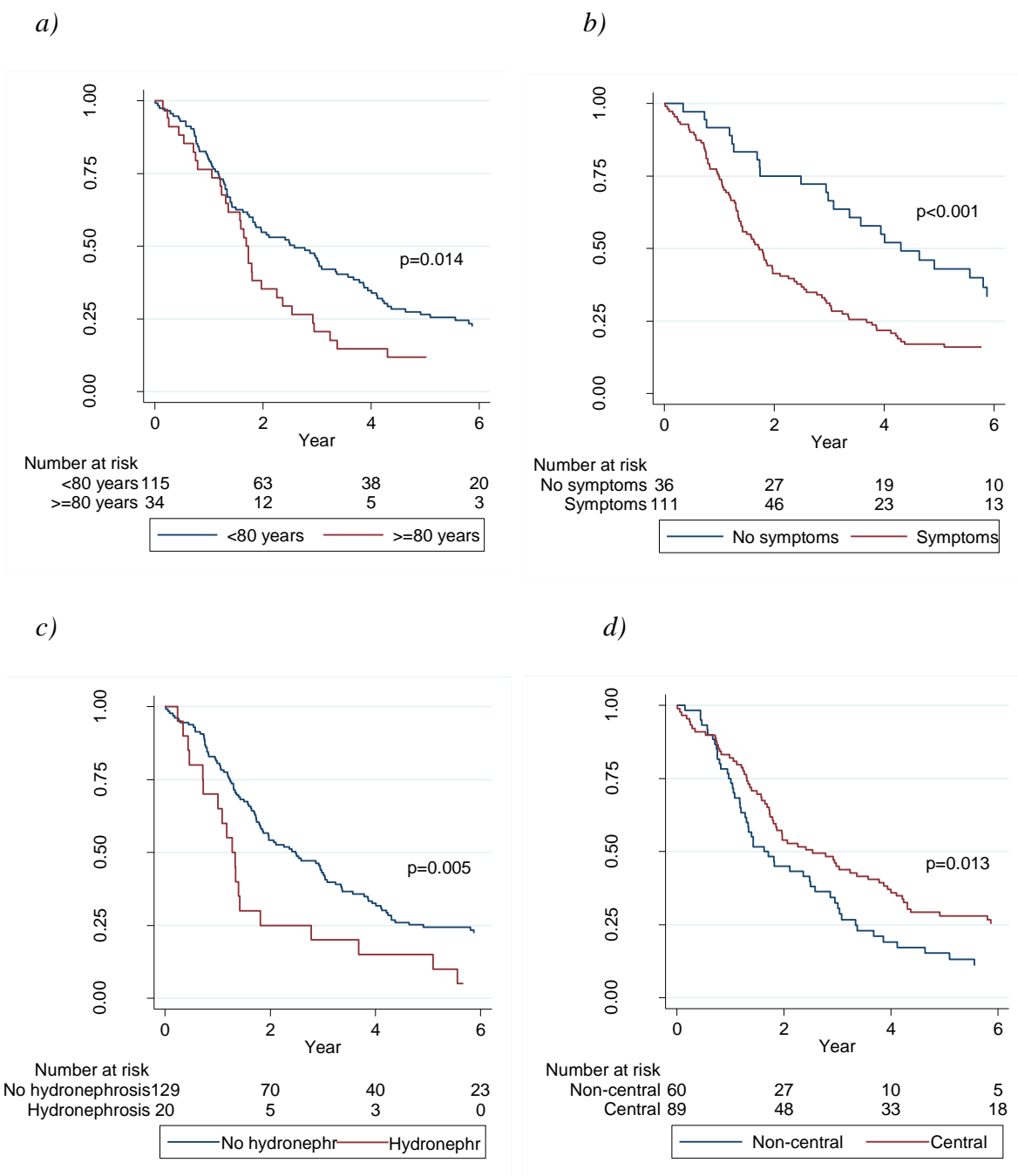


Figure 17 Survival of patients treated with curative intent according to a) age, b) presence of symptoms at time of diagnosis, c) presence of hydronephrosis and d) location of the local recurrence, n=149



4.3 PAPER III

4.3.1 Characteristics

The characteristics of all 426 patients of study III are illustrated in *Table 6* and *7* and are more thoroughly described in the characteristics section of paper II. In this study, 221 patients were aged <75 years and 205 patients were aged ≥ 75 years. 117 patients (27.5%) had their LRRC diagnosed during period 1 (1995-1998), 204 (47.9%) got a diagnosis in period 2 (1999-2002), and 105 (24.6%) during period 3 (2003-2007).

4.3.2 Treatment and resection margins

Of the 149 patients treated with curative intent, 63 (42.3%) received neoadjuvant treatment and of these 41 received RT, 18 had CRT and four received ChT only (*Table 10*). 121 (81.2%) patients were operated with tumour resection, 19 patients (12.8%) had explorative laparotomy only and nine patients (6.0%) were never operated, due to aggravated general condition, tumour growth during neoadjuvant treatment, patient refusal to surgery or death.

Of the 121 patients resected with curative intent, 64 (52.9%) had an R0-resection, 31 patients (25.6%) had an R1-resection and 26 (21.5%) had an R2-resection. 25 patients (20.7%) received adjuvant chemotherapy. Patients with a non-central location of the LRRC had a five times higher risk of a non-radical (R1/R2) tumour resection compared with patients with a central tumour location (OR 5.02, 95% CI: 2.25-11.21).

4.3.3 Time periods and regions

There was a decrease in the proportion of patients treated with curative intent in period 3 compared with the previous periods but the difference was not significant. A higher proportion of patients were operated with R0-resection during period 2 compared with period 1 and 3 but this difference was not significant either. The proportion of patients with central recurrence decreased over time, from 52% in period 1 and 54% in period 2 to 39% in period 3 ($p=0.033$).

Regarding regions, the rate of patients with LRRC as first event varied between 3.4 to 5.8% and the overall national rate was 4.7%. The rate of patients treated with curative intent varied between 29% and 43% but the differences were not significant.

Table 10 Treatment characteristics of patients treated with curative intent, n=149

	Number (%)
Neoadjuvant treatment	
(C)RT	59 (39.6)
CT	4 (2.7)
No treatment	84 (56.4)
Data missing	2 (1.3)
Surgery	
Tumour resection	121 (81.2)
Explorative laparotomy	19 (12.8)
No surgery	9 (6.0)

4.3.4 Follow-up and survival

Five-year survival for patients resected with curative intent was 43% after R0-resection, 14% after R1-resection and 4% after R2-resection (*Figure 18*). The most common type of first failure was distant metastases, affecting 30% of the R0-resected patients and 42% of the R1-resected patients. Local re-recurrence was significantly more common in R1-resected patients, where 29% were affected, compared with 20% of the R0 resected patients (p=0.044).

The risk of any failure, including re-recurrence, distant metastases or death, for R0/R1-resected patients was significantly affected by margin status. R1-resected patients had a doubled risk of failure compared with R0-resected patients in an adjusted analysis (HR 2.04, 95% CI: 1.22-3.40). No significant associations to age, sex, time to LRRC or location of the LRRC were found.

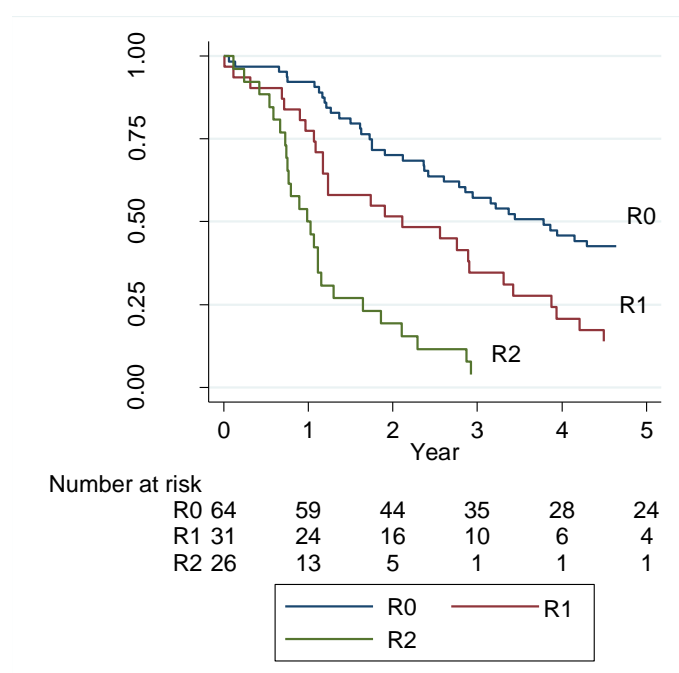


Figure 18 Survival for patients operated with tumour resection with curative intent

4.4 PAPER IV

4.4.1 Characteristics of treatment groups

Of all 426 patients, 149 (35.0%) patients were treated with tumour resection, 193 (45.3%) received treatment without tumour resection and 84 (19.7%) received best supportive care (*Figure 13*).

The patients treated with tumour resection were significantly younger (median 71.9 years) than patients treated with best supportive care (median 79.9 years) ($p < 0.001$).

Fewer of the patients treated with tumour resection were symptomatic (75.2%), compared with the other two groups (90.2% and 88.1%) ($p < 0.001$). The most common symptoms among the patients treated with tumour resection were anal or perianal symptoms (21.5%), followed by change of bowel habits (20.1%) and pain (18.8%). On the contrary, pain dominated as the most common symptom both among patients treated without tumour resection (39.4%) and patients treated with best supportive care (31.0%). In total, 130 (30.5%) of all patients had symptoms of pain. A majority of these (58.5%) were treated without tumour resection and most of the patients with pain (63.1%) also had a non-central location of the LRRC.

4.4.2 Surgical treatment

The 149 patients operated with tumour resection were assessed in 50 different hospitals and the surgery was performed in 48 hospitals, with a range of 1 to 23 operated patients per hospital during the study period.

Abdominal resection was performed in 132 patients (88.6%) (*Table 11*). 84 patients (56.4%) were operated with a resection of the neorectum and in 49 of these, additional organs were resected simultaneously. APR was the most common procedure, performed in 65 (43.6%) of the resected patients, followed by HA (10.7%) and PE (8.7%). Only 12 patients (8.1%) received IORT. Reconstructive surgery was performed in 18 patients (12.1%) and the most common type was a reconstruction of the urinary tract, valid for 11 patients. 67 patients (45.0%) had local R0 surgery, but only 64 (43.0%) received a curative treatment.

In the 193 patients treated without tumour resection, 79 patients (40.9%) were treated with surgery, where creation of a stoma was the most common procedure.

Table 11 Surgical details for patients treated with tumour resection for local recurrence, n=149

Variable	Number (%)
Surgery	
Abdominal resection	132 (88.6)
Total pelvic exenteration	13 (9.8)
Colorectum/neorectum only	35 (26.5)
Colorectum/neorectum + other organ	49 (37.1)
Other organ only	35 (26.5)
Resected other organ*	
-small bowel	36
-vagina/vulva	22
-internal genitals#	15
-soft tissue	13
-sacrum/coccyx	8
-colon	5
-urinary tract organs	4
-iliac lymph nodes	1
-pelvic wall	1
Local excision	17 (11.4)
Resection margins	
R0	67 (45.0)
R1	32 (21.5)
R2	50 (33.5)
Curative surgery	
No	85 (57.0)
Yes	64 (43.0)

4.4.3 Complications

Early postoperative complications (<30 days after surgery) were common and found in 83 of all 228 operated patients (36.4%). The frequency was significantly higher among patients treated with tumour resection than among those operated without tumour resection (41.6% vs 26.6%, $p=0.022$). Still, the non-resected patients had a significantly higher postoperative mortality (10.0% vs 2.4%, $p=0.002$). The most common surgical complications among patients treated with tumour resection were intraabdominal abscess, wound infection, anastomotic leakage, bleeding and fistula. Among the non-resected patients, ileus, anastomotic leakage and bleeding were most common.

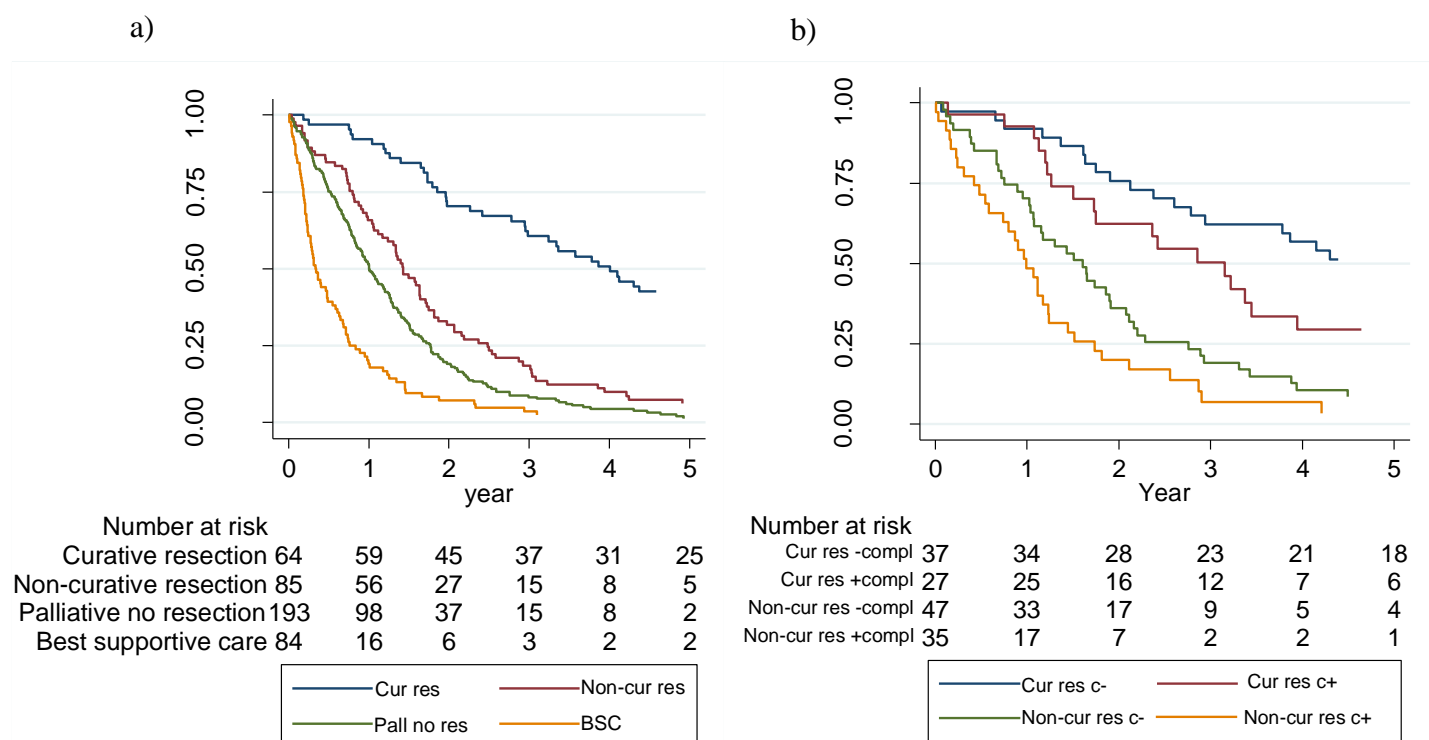
Late complications (≥ 30 days after surgery), occurred in 35 (54.7%) of the curatively operated patients and pain was the most common problem.

4.4.4 Follow-up and survival

Three-year survival was 60.6% for patients treated with a curative tumour resection, 18.6% after non-curative resection and 8.3% after treatment without tumour resection (*Figure 19a*).

Among patients receiving surgical treatment, presence of postoperative complications was associated with a worse survival. However, a curative treatment was more important than absence of complications, since curatively operated patients with postoperative complications had a better survival than non-curatively resected patients without complications (*Figure 19b*).

Figure 19 Kaplan-Meier plots illustrating overall survival in a) all patients, according to type of treatment (n=426), b) all patients receiving curative and non-curative surgical treatment, according to complication status (n=224)



5 DISCUSSION

Many changes in management and treatment of patients with primary RC have been implemented during the last decades, including improved preoperative staging with MRI, the TME-technique, preoperative RT in selected patients, MDT conferences and follow-up programs. These changes have resulted in a marked decrease of the LRRC rate and a major improvement of the survival rates for patients with RC. According to the SCRCR, the relative five-year survival for patients with RC is today 80% for stage I-III¹. However, 5-15% of the patients suffer a LRRC and 20-25% get distant metastases after radical primary surgery and for these patients, symptoms are severe, prognosis is poor and treatment options are few. The choice may stand between a potentially curative outcome at the cost of half the pelvis and one limb or a palliative treatment with severe pain, complicating perineal fistulas and a short life expectancy. This is a tough decision for both the patient and treating surgeon and therefore it is essential that there are good, evidence-based grounds for the treatment decision.

5.1 TIME TO LRRC

Time to LRRC was not a prognostic factor for LRRC survival in the registry-based study (study I). The lack of influence of this variable was confirmed in the following studies based on data from medical records, as no impact was seen on the selection for curative treatment (paper II) or the risk of any failure in R0/R1 resected patients (paper III). In paper IV, it was significantly more common for patients with LLR to be treated without tumour resection than to have a tumour resection (60% vs 40%, $p=0.034$). This analysis was however univariable, the significance was small and the result must be interpreted with caution. It has been hypothesised that patients with ELR have a worse prognosis than patients with LLR, possibly as they are less likely to have had RT or due to a more aggressive tumour type in patients with ELR²⁴⁴⁻²⁴⁷. An early diagnosed LRRC could also imply a more extensive residual microscopic tumour spread than in late recurrences. Other reports have however not shown any impact on prognosis of this variable²⁴⁸⁻²⁵¹. In summary, the results of the papers of this thesis establish that time to LRRC did not influence neither the selection for treatment nor the outcome of treatment.

5.2 PREDICTIVE FACTORS FOR TREATMENT INTENTION

An optimal selection process for treatment with curative intent necessitates a complete assessment, adequate staging and discussion at an MDT conference. 80% of the patients in study II-IV were assessed with CT or MRI, which means that every fifth patient did not have an acceptable local preoperative assessment. It may be expected that some patients have an affected general condition and are not suitable for either curative or palliative treatment and a complete assessment may therefore have been bypassed in these cases. The annual report from the SCRCR 2016 reported that more than 95% of all patients with primary RC were discussed at a preoperative MDT conference during 2016¹. Unfortunately, information about how many

patients that had been discussed at MDT meetings for their LRRC could not be extracted from the medical records in a reliable way, but it is not likely to be as high as 95%. Regarding this, it seems that there is room for improvement of the preoperative routines for patients with LRRC.

In study II, it was found that advanced age, advanced primary tumour, previous APR or HA surgery, presence of symptoms (pain in particular) and a non-central tumour location were predictive factors for treatment with palliative intent. These findings are not very controversial, as these factors have previously been shown to be associated to a worse prognosis^{152,247,252}. It was however surprising that there was no correlation to co-morbidity, as a high co-morbidity may be an obstacle to surgery. One explanation to this might be that there are several methods to report co-morbidity. The Charlson comorbidity index was developed to allow for a useful classification of co-morbidity in risk-analyses in longitudinal studies²⁵³. Both presence and severity of a condition is valued and assigned a weighted index (1, 2, 3 or 6), which is summarised in each patient. The ASA (American Society of Anaesthesiologists) physical status classification system is more complex and provides a staging (I-VI) of a patient's current status in relation to the planned surgical procedure²⁵⁴. None of these methods were used in the studies of this thesis, as it was difficult to interpret this information from the medical records.

Only 14% of the patients with LRRC were asymptomatic and detected at planned screening visits (paper II-IV). It would be relevant to assess if a screening programme, aimed at early detection of LRRC in high risk patients, could result in a potentially curative treatment in a higher proportion of patients. The US Multi-Society Task Force on Colorectal Cancer suggests local surveillance with flexible sigmoidoscopy or endoscopic ultrasound every 3-6 months during the first 2-3 years in patients with an increased risk of local recurrence after treatment for primary rectal cancer. However, the evidence for an improved survival with this management is low and randomised controlled trials are lacking²⁵⁵. In addition, the rate of anastomotic LRRC detectable with endoscopy is probably low after appropriate TME surgery. A regular follow-up with pelvic MRI in high risk patients may be more appropriate with an enhanced chance of early detection of pelvic recurrences²⁵⁶.

5.3 TIME TRENDS

Several studies have illuminated the advantages of a multidisciplinary management in complex diseases, both in terms of selection for treatment and treatment results^{57,58,257}. Kontovounis et al showed a decrease in the proportion of patients operated on for LRRC from 36% to 28% between 2010 and 2014⁶⁰. The same trend was seen in our material (38% to 29%), but the difference was not significant. It is possible that this indicates a trend towards a more thorough selection of patients for surgery in recent years, possibly through an increased MDT management. If this is the case, it would also imply rising R0 resection rates. This could not be seen in our material, possibly due to a power problem or too narrow time intervals, but it may also be that the full effect of the more thorough selection for treatment has not yet been seen.

A time trend that however was seen in study III was an increased rate of non-central recurrences over time. This trend has been observed in previous studies and may also influence the selection for treatment as posterior and lateral recurrences are more difficult to operate¹⁵⁸⁻¹⁶⁰.

5.4 TREATMENT OF LRRC

One third of the patients with LRRC were treated with abdominal tumour resection (study IV) and of these, only 10% were treated with PE despite a non-central tumour involvement in 40% of the resected patients. LRRC tumours with a non-central location have the worst prognosis and are the most challenging to operate, requiring extended excisions¹⁷⁶. The results of the present studies however indicate that some patients may not have received adequate surgical treatment. The reasons for this are unknown, but insufficient preoperative staging, lack of multidisciplinary competence and an overall pessimistic view of the condition LRRC are possible explanations. There are few previous population-based studies to compare our results with and none with a nation-wide perspective^{124,125}. Smaller population-based studies, covering limited regions, have shown similar resection rates, but a review article from 2009 including 19 papers on LRRC, revealed higher resection rates, between 40-50%²⁰². The represented studies were almost exclusively performed in highly specialised centres, which entails a risk of selection bias.

In total, 29% of the patients resected with curative intent had not received RT, neither during the primary nor recurrent disease (study III). This is a surprisingly large proportion and reasons for this may be the lack of uniform treatment guidelines and MDT approach. Although few studies have evaluated the effects of RT or CRT specifically on LRRC, there is forceful evidence of the beneficial prognostic effect of RT on pelvic cancer^{61,258,259}. According to the Beyond TME collaborative group, preoperative CRT is today recommended to all patients with LRRC, unless there are contraindications¹⁵⁰.

Centralisation of the management of complex diseases to highly specialised centres in order to improve the prognosis has grown parallel to the increased MDT strategy. A study of patients with oesophageal cancer showed that a centralisation of surgery led to an unchanged number of complications but a significant increase in survival²⁶⁰. It is however difficult to point out a specific factor playing the crucial role in these results. In the case of LRRC there is reason to believe that the access to multiple disciplines and other resources play a crucial role and the unit's overall accumulated experience may be more important than that of the individual surgeon.

5.5 METHODOLOGY

The main strengths of the four papers are that they are population-based, covering a nation-wide cohort with a long follow-up time. To our knowledge, paper IV is the first nation-wide study reporting detailed data on the surgical treatment of LRRC. Studies II-IV also have the

advantage of being based on validated data from medical records, moreover including a survey of multiple new variables, not previously reported to any registry.

Of course, there are also some limitations. Firstly, since the selection of patients with LRRC for all four studies is based on the diagnoses reported to the SCRCR, the risk of underreporting must be taken into account. Jörgren *et al.* showed that there was a discrepancy of 11% between the registry and medical journals regarding the reporting of LRRC diagnosis. This analysis was based on the LRRC diagnoses actually reported to the registry and provides no information about how many patients with LRRC that were not reported. It is difficult to assess the proportion of patients that may have been missed, but it is a reasonable guess that these patients are few and mainly consist of those with very late recurrences or a very poor general condition. Secondly, a review of a large number of medical records entails the risk of misclassifications due to misinterpretations. Since the whole review was made by the same person, these errors could be either sporadic or systematic. In order to avoid systematic errors, regular reconciliations were held with the research team, but minor sporadic errors may have occurred. These should however be few and of minor statistical importance. Thirdly, all four studies are performed on the same cohort of patients which introduces the risk of multiple significance problems. This is a well-known statistical problem, which implies an increased risk of false positive results (type I errors) when performing a large series of analyses on the same group of patients²⁶¹. Hence, it is possible that some of the values of the studies do not reflect a true statistical significance but, in fact, are results by chance. Regarding this, caution should be taken while interpreting individual values. Finally, despite the population-based large cohort, the lack of significance in some of the analyses may be due to a power problem, leading to type II errors. This is especially valid for the subgroup analyses with smaller analysed groups.

6 CONCLUSIONS

Overall conclusion

A minority of patients with LRRC were treated with curative intent and resection surgery was performed at a high number of surgical centres. A curative resection of the LRRC is essential for a favourable prognosis. There is room for an enhanced multidisciplinary management of these patients, which could result in better selection for curative surgery.

Specific conclusions

Time to LRRC had no impact on survival calculated from diagnosis of LRRC. All patients should be assessed for potential curative surgery, disregarding time to LRRC.

A minority of the patients with LRRC were treated with curative intent. Positive predictive factors for treatment with curative intent were young age, AR at primary surgery, a low stage of the primary tumour, absence of symptoms, absence of hydronephrosis and a central location of the LRRC. The same factors were associated with a favourable prognosis among patients treated with curative intent.

There were no significant time trends or regional differences regarding the selection for treatment with curative intent or the proportion of completely resected tumours. There was however a significant increase in the proportion of patients with a non-central LRRC over time and these patients also had a higher likelihood of non-radical tumour resection. The prognosis was poor for all patients with LRRC, but nearly half of the patients treated with radical tumour resection survived five years.

Surgical resection of the LRRC was performed in a minority of the patients and APR was the most common resection procedure. Less than half of the patients were treated with multi-organ resection. Complications were common and were associated with an inferior survival rate.

7 FUTURE PERSPECTIVES

Many issues concerning LRRC are still to be investigated. Since TME-surgery, modern RT treatment and routines for multidisciplinary management were successively implemented during the study period of the papers of this thesis, the full effect of this management has not yet been shown. Therefore, it would be interesting to investigate what factors that predict treatment with curative intent in a more recent cohort, where modern rectal cancer treatment has been practiced in full. It would also be interesting to find out what types of procedures that are performed today and whether the trend of an increasing rate of non-central recurrences persists.

It has previously been indicated that women receive RT to a lower extent than men in primary RC²⁶². Another study of patients with RC has shown a lower risk of death in married patients and patients with high incomes²⁶³. No differences between sexes in the selection for treatment were found in the studies included in this thesis, but it is possible that factors like educational level, income level or civil state have an influence on the selection for treatment of LRRC. This will be investigated for the cohort included in paper II-IV, with additional data from Statistics Sweden.

There are also other factors that may influence the outcome of surgery. It would be interesting to go even further in the investigation of what factors may predict radical surgery of a LRRC. A study of whether MRI-findings may predict complete or incomplete tumour resection has been initiated in a recent Stockholm material. This study may give additional information about what patients may receive the greatest benefit from LRRC surgery. A study of the current surgical treatment of patients with LRRC at a tertial referral centre (Karolinska University Hospital) has been completed by our research group and will be published shortly.

A decreasing proportion of patients treated with curative intent entails an increasing number of patients not having curative surgery. What happens to them? What is their quality of life? A more thorough investigation of the given palliative treatment in patients with LRRC and their QoL would give important information about this specific group of patients.

8 SAMMANFATTNING PÅ SVENSKA

Cancer i tjock- och ändtarm (kolorektalcancer) är den tredje vanligaste cancerformen i världen och drabbar årligen 1,4 miljoner människor. Av dessa utgörs en tredjedel av cancer i ändtarmen (rektalcancer), vilket drabbar cirka 2000 svenskar varje år. Sjukdomen drabbar i huvudsak äldre och medianåldern vid diagnos är 72 år. Ändarmscancer behandlas genom kirurgiskt borttagande av ändtarmen och därefter sammankoppling av de kvarvarande tarmändarna alternativt stomi. Prognosen för patienterna har förbättrats markant under de senaste decennierna, beroende på flera faktorer: En förbättrad kirurgisk metod (s.k.TME), där fettskiktet intill ändtarmen tas bort tillsammans med tumören, introducerades i början av 90-talet, vilket ledde till förbättrade resultat. Tillägg av strålbehandling med eller utan kombinerad cellgiftsbehandling före operation av tumören minskar ytterligare risken för tumöråterfall. Införandet av ett multidisciplinärt omhändertagande (MDT), där fynd och behandling rörande varje patient diskuteras mellan onkolog, kirurg, patolog och radiolog vid särskilda behandlingskonferenser har ytterligare bidragit. En standardiserad utredningsgång med magnetkameraundersökning (MRI) för bedömning av lokal tumörutbredning och datortomografi (CT) för att påvisa eller utesluta fjärrspridning har lett till en förbättrad gradering av tumörutbredning. Standardiserade uppföljningsprogram efter behandling har också införts, i syfte att hitta eventuella återfall på ett tidigt, behandlingsbart stadium.

Ett lokalt tumöråterfall, så kallat lokalrecidiv (LRRC), innebär en återväxt av tumör i lilla bäckenet efter tidigare botande kirurgisk behandling. LRRC drabbar idag ca 5-9% av de som tidigare opererats för primär ändarmscancer, jämfört med 30-40% för 30 år sedan. Vanliga symptom vid såväl primär RC som LRRC är blod i avföringen och ändrade avföringsvanor. Vid LRRC kan man dessutom få blödningar från slidan, smärta runt ändtarmen och urinträngningar. Utredning görs vanligen med magnetkameraundersökning (MRI) för lokal tumörgradering, skiktröntgen (CT) för att utesluta fjärrmetastaser och vävnadsprov (biopsi) från tumören för att bekräfta diagnosen. Fynden diskuteras därefter vid MDT-konferens. Beroende på lokaliseringen av patients LRRC krävs olika typer av behandling, men nationella riktlinjer för behandling av LRRC saknas i Sverige. Ett kirurgiskt ingrepp med borttagande av hela tumören är den enda chansen till bot. En behandling med botande syfte (kurativ intention) kan innebära borttagande av kvarvarande ändtarm, men ibland även borttagande av livmoder, äggstockar, prostata, urinblåsa, del av korsbenet (sakrektomi), och halva bäckenbenet (hemipelvektomi). I vissa fall är operation inte möjlig på grund av alltför omfattande lokal tumörväxt, inoperabel fjärrspridning eller andra komplicerande sjukdomar. I dessa fall kan det bli fråga om bromsande (palliativ) behandling eller enbart symptomlindrande åtgärder (best supportive care, BSC). Skillnaden är stor vad gäller överlevnad för de patienter som genomgår en botande operation och de som inte gör det. Av de som genomgår botande kirurgi kan upp till 60% överleva i fem år, medan motsvarande siffra för alla LRRC-patienter sammantaget är under 10%. Sjukdomen

innebär dessutom ofta svårt lidande för de drabbade med blödningar, smärta och återkommande infektioner.

Syftet med denna avhandling var att studera hur patienter med LRRC i Sverige utreds, behandlas och vilken prognos de har.

I **arbete I** undersöktes huruvida tiden mellan operation för primär ändtarmscancer till diagnos av LRRC hade någon betydelse för överlevnaden räknat från upptäckten av LRRC. Data rörande patienten, primärtumören, tidpunkt för LRRC diagnos och uppföljning inhämtades från Svenska Kolorektalcancerregistret (SCRCR), som är ett nationellt register dit alla diagnoser av ändtarmscancer och LRRC rapporteras. Samtliga patienter som opererats för primär ändtarmscancer mellan 1995-2002 och fått ett LRRC inom 5 år inkluderades och analyserades. Totalt inkluderades 386 patienter. Resultaten visade att tiden till LRRC inte hade någon betydelse för överlevnaden. Däremot var överlevnaden bättre vid låg ålder, mindre avancerat stadium på primärtumören och kirurgiskt borttagande av patients LRRC.

Arbete II syftade till att undersöka vilka faktorer som ligger till grund för valet av kurativt syftande behandling kontra icke-kurativt syftande behandling (palliativ eller BSC) hos patienter med LRRC. Liksom i arbete I inkluderades de patienter som opererats för primär ändtarmscancer mellan 1995-2002, men denna gång inhämtades uppgifterna från journalkopior från behandlande sjukhus och antalet inkluderade patienter skiljde sig därför från arbete I. Journalerna granskades både med avseende på egenskaper hos och behandling av primärtumören och med inhämtande av uppgifter om LRRC. Felregistrerade patienter uteslöts. Totalt 426 patienter inkluderades, varav en dryg tredjedel (35%) erhöll behandling med kurativ intention. Faktorer som ökade sannolikheten för detta var låg ålder, symptomfrihet vid diagnos och ett LRRC enbart beläget i tarm, urinvägar eller inre könsorgan. Vid undersökning av enbart de patienter som behandlats med kurativ intention, så innebar förekomst av dessa faktorer en förbättrad överlevnad. Av de som behandlats med kurativ intention överlevde 23% i fem år eller mer, medan motsvarande siffra var 9% för alla patienter med LRRC.

I **arbete III** undersöktes om det fanns några skillnader mellan tidsperioder eller behandlande regioner avseende behandlingsintention eller resultatet av kirurgin. Samma 426 patienter som ingick i arbete II analyserades. Resultaten under tre tidsperioder (1995-1998, 1999-2002, 2003-2007) och i 6 behandlande regioner jämfördes. Varken region eller tidsperiod påverkade valet av behandlingsintention eller resultat av kirurgin (radikalitet). Däremot hade andelen patienter med LRRC utanför tarm, urin- och könsorgan ökat över tid och dessa löpte högre risk för en icke-botande (icke-radikal) operation. För dem där ett fullständigt (radikalt) borttagande av tumören kunde uppnås var överlevnaden god, 43% överlevde i minst fem år, jämfört med de patienter där operationen var icke-radikal, där överlevnaden var 14%.

I **arbete IV** undersöktes den givna behandlingen närmare hos samma patienter som inkluderats i arbete II och III. En tredjedel (35%) behandlades med kirurgiskt borttagande av LRRC. Hos

dessas var borttagande av del av tarmen det vanligaste ingreppet. En tiondel av patienterna genomgick borttagande av samtliga organ i lilla bäckenet (del av tjock/ändtarm, urinblåsa, inre könsorgan), så kallad total bäckenutrymning. En femtedel av patienterna opererades i symptomlindrande syfte utan borttagande av tumör, så kallad palliativ operation. Detta utfördes oftast i form av uppläggning av stomi på grund av tumörorsakat tarmhinder.

Operationsorsakade komplikationer var vanliga och medförde en sämre prognos både hos de som opererats med kurativ respektive icke-kurativ intention. Den viktigaste faktorn för en god prognos var dock ett radikalt borttagande av LRRC.

Sammanfattningsvis så visar denna avhandling att en minoritet av patienterna med LRRC i Sverige behandlades med kurativt syftande behandling och att ett radikalt borttagande av LRRC är nödvändigt för en god prognos. Tid till recidiv hade ingen betydelse för prognosen hos patienter med LRRC, varför denna faktor inte bör räknas med vid ställningstagande till behandling. Flera faktorer hade betydelse för urvalet av patienter för kurativt syftande behandling och samma faktorer hade även betydelse för överlevnaden, varför urvalet tycks vara adekvat. Kirurgisk behandling av LRRC är komplex och kan kräva kunskap och engagemang från flera kirurgiska specialiteter. Det multidisciplinära omhändertagandet kan sannolikt utvecklas ytterligare, vilket kan leda till färre komplikationer och bättre överlevnad.

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